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RELATION OF CLIMATE TO RESPIRATORY ALLERGY

DAVID ORDMAN, B.A., M.B., Ch.B. (Cape Town), D.P.H. (Rand), F.A.C.A.
Johannesburg, South Africa

IT IS OBVIOUS that climate has an *indirect* effect on the causation of respiratory allergy because specific vegetation types are associated with particular climates. Seasonal pollinosis is thus a reflection of the plant life in a particular region at a certain time of the year. Similarly, respiratory allergy may occur in only certain months of the year when summer or other seasonal fruits have been eaten. Insect species also characteristically flourish under certain climate conditions, and persons sensitized to the emanations from these insects manifest symptoms when they appear. In South Africa, for example, allergic vasomotor rhinitis and bronchial asthma have resulted from the inhalation of the dust of the friable dead bodies of *Psychoda* spp. present in great numbers in the summer season at some of the local sewage disposal works.[1]

It is a common assumption that climate has a *direct* etiological bearing on the occurrence of symptoms of nasal allergy and bronchial asthma. There is considerable literature relating to this subject, and every physician is able to point to cases where the aggravation of symptoms in his patients appears to correspond with certain types of weather change. It is frequently reported that some climates are "good" and some "bad" for asthmatic patients. Most of these statements, however, are the results of impressions rather than of controlled bioclimatological investigations. Temperature and barometric pressure changes, winds, atmospheric humidity and other such factors have variously been incriminated as the direct agents in the provocation of symptoms in the patient. Frequently the evidence regarding these factors is con-

From the South African Institute for Medical Research.
Dr. Ordman is Lecturer in Immunology at the University of Witwatersand.

flicting and, in any event, no basic principles connecting climate and respiratory allergy have so far emerged.

Floyer,[2] in 1698, stated that asthmatic attacks were precipitated by changes of weather, especially by fall of barometric pressure. He thought that dry air was best for the asthmatic patient but mist or moist air was bad. The east wind which brought dampness and mist was also bad for the asthmatic patient who was affected not by the rain itself but by the watery vapors that for a few days preceded it.

Nearly a century ago, Salter[3] described as detrimental to asthmatic patients damp, low altitude situations which abound with vegetable life. Solly,[4] in 1897, declared that the one meteorological element which had the most marked effect on asthma was either a decided increase or decrease in barometric pressure. On the other hand, Leopold and Leopold[5] thought that change of barometric pressure or relative humidity did not have much effect on the clinical symptoms. They observed two asthmatic patients in a dust-free, air-conditioned room and thought that symptoms were aggravated by atmospheric conditions preceding a storm or sudden drop in temperature due to increased wind velocity which (they suggested) increased the amount of air-borne substances reaching the patients. Nelson and coworkers[6] studied ragweed asthmatic patients in a filtered, air-conditioned room and found that all developed asthma on a day of unstable weather, characterized by sudden drop of temperature, marked rise in humidity and a sharp drop in barometric pressure. Evers and Schultz[7] investigated 500 patients and concluded that dry air and great variations of temperature were harmful to asthmatics. Tuft,[8] summarizing available information regarding climate and asthma, stated that the important factors in precipitating symptoms appeared to be extremes or sudden changes of temperature, cold winds and excessive humidity. He thought it likely that physical allergy might be important in this group and quoted Duke,[9] who believed that marked or sudden changes of temperature produced symptoms in many respiratory allergy patients, possibly because of non-specific exaggerated physiological action. Mohr,[10] investigating fifty-two children, found that half the attacks of asthma took place when there was a change from the prevailing west wind to an east wind, but he did not find any relation between attacks and variations in relative humidity and barometric pressure. Yogi[11] found in Formosa that there was a much higher incidence of asthmatic attacks in the wet season and attributed this to the increased relative humidity. Feige and Rosenbaum[12] found no unusual weather conditions when children with chronic asthma developed severe attacks. Anglad[13] also thought that meteorological factors did not modify the intensity, frequency or intervals of attacks in eighty asthmatic children. Feinberg,[15] summarizing the current views on the subject, stated that weather played a prominent part in the clinical attacks of respiratory allergy, but found it impossible to decide which among the numerous factors including temperature changes, electrical storms, falling barometer, strong winds, lightning or rain was important.

Climate in a non-specific manner apparently affected the individual favorably or adversely, depending upon the type of climate and on the particular individual. He suggested that in some way certain of these physical factors might also act as primary physical agents. Although change of climate was one of the oldest therapeutic methods for asthmatic sufferers, Feinberg pointed out that for every one who derived benefit from such change, many others did not. He thought, however, that metabolic changes occurring with a change of climate might have a favorable influence on asthma. Although he accepted the idea that weather and climate factors had profound effects on allergic symptoms, he wondered whether they were specific causes of allergic diseases. Such factors, particularly rain storms, strong winds and damp weather, probably produced symptoms by influencing respiratory physiology.

Rosen,[16] discussing bronchial asthma and the weather on the basis of a study of asthma patients in an army hospital over a period of four months in the non-pollinating season, thought that sharp changes in the outdoor weather (even though indoor weather might change little) seemed to cause more attacks of asthma. Low indoor humidity and drop in outdoor temperature seemed to be important factors. He admitted, however, that it was impossible to pick on one or two weather factors as a cause since weather is a combination of all the atmospheric forces. He suggested that these conditions might influence the absorption of allergens from the nasal mucosa as a result of chemical, nervous and endocrine reactions through the autonomic nervous system. Klotz and Bernstein[17] argued that it was the sudden cooling effect which made strong winds unfavorable to sufferers. They suggested that damp air and fog provoked attacks because of the increased breathing resistance that moisture imparted and because of the suspended solid particles in the air during fog. Swartz,[18] in explanation of the finding that a falling barometric pressure adversely influenced asthma, suggested that the already labile vascular bed of the bronchial mucosa dilated with the sudden drop in external pressure. As a result, there was exudation and narrowing of the bronchial lumen with secondary effects (dyspnea, mucus secretion and accumulation, as well as muscular spasm) which resulted in clinical asthma. He suggested also that a marked increase in humidity had a bad effect on the asthmatic patient because it interfered with surface evaporation. This interference led to an increase in the respiratory rate and lowering the blood CO_2 with a resulting alkalosis.

The "aran" hypothesis of Curry,[19] now largely abandoned, had a considerable vogue, and its application to bioclimatology has stimulated much thought and work on the influence of climate on health. Aran is a molecule of oxygen with more than three atoms, probably similar to ozone. Curry reported that physical feeling differed in different aran atmospheres; disturbances of well-being occurred with the diminution of aran to 30 to 50 per cent, but "cold front" symptoms were present when the aran value was high. Buettner[20] pointed out how the Föhn wind had been blamed for

centuries, but without adequate explanation, for its adverse effects on man. Wind has nearly always been regarded as a contributory source of human ills, and Martin[21] quoted in this connection the Sirocco of Sicily, the Salano of Spain, the Zonda of the Argentine, in addition to the Föhn winds of the Alps, all of which are considered detrimental to either physical or mental health.

Although the above clinical impressions of the relation of respiratory allergy to climate are often contradictory, there nevertheless probably exists a unifying factor which could reflect an element of truth in each of these various opinions. While there is little doubt that climate changes play a part in the aggravation or amelioration of symptoms, the question remains whether climate itself is responsible for the initiation or the direct activation of respiratory reactions in an allergic subject or whether the effect is indirect with one or more mediating agents between the external physical climate and the body tissues. If the effect of climate action is indirect, it becomes necessary to consider the nature of such possible intermediate agents.

Climate or climate change is made up of a combination of so many diverse elements of such varying complexity that it is difficult to look upon it as a unity which, in itself, could precipitate symptoms in an allergic subject. Further, in the same way that climate changes are known to exacerbate or ameliorate the patient's complaint in certain general diseases (e.g. "rheumatism"), so also might respiratory allergic conditions be affected. In other words, there would appear to be something other than a true climate "allergen" in the provocation of symptoms. It is for these reasons that a useful approach to the study of climate in relation to respiratory health appears to lie in the understanding of the physiological effects of the various individual climate factors and in the search for some intermediate agent or agents influenced by or accompanying certain climate conditions.

Three possibilities are considered regarding the relation of climate to respiratory allergy:

1. Climate or climate change acts as an *irritant* and, like any other irritant, is able to provoke symptoms in a basically allergic person.

2. Under certain specified climate conditions the local *house dust* is rendered more allergenic. A susceptible patient is therefore affected not directly by the climate itself but indirectly by the allergenically potent house dust.

3. The adverse "climate" effect on the allergic patient is due not to gross climate factors like temperature, humidity, barometric pressure, et cetera, but to the state of atmospheric ionization, both qualitative and quantitative, existing in his environment at the time.

CLIMATE, AS AN "IRRITANT", PROVOKES RESPIRATORY SYMPTOMS IN ALLERGIC SUBJECTS

It is generally accepted that the allergic tendency in a person is an inborn characteristic and that symptoms are made manifest in exogenous allergy by

some specific "trigger" factor such as pollens, animal dander, feathers, house and industrial dusts, foodstuffs and drugs, or in endogenous allergy by "stress," which is associated with a variety of complicating non-specific influences such as physical, infective, endocrine and psychological factors.

Insofar as physical factors are concerned, it is not uncommon for a patient suffering from respiratory allergy to experience an aggravation of his nasal or chest symptoms when driving on a dusty road or as he inhales by chance the fine quartz dust blown from the sand dumps on windy days in the gold mining areas of Johannesburg. However, symptoms resulting from the occasional inhalation of siliceous dust must be regarded as having an irritative and not a specific allergenic effect. A similar exacerbation of symptoms is often seen in basically allergic persons from the inhalation of perfumes, petrol and diesel engine fumes, coal, wood or cigarette smoke, smog, etc. Chilling or overheating of the body results in vasoconstriction or vasodilitation and may thus also be regarded as a form of irritating agent. It is in this sense that climate change is an irritant which, like any other irritant, provokes respiratory symptoms in a fundamentally allergic person, and there is thus no need to postulate any intermediate agent. It is interesting that Klotz and Bernstein[17] considered the possibility that weather and environment were stress factors that could react on an individual and his tissues and produce alterations of the autonomic nervous system, endocrines and body-fluid chemistry including the pH, K/Ca balance, and the immune processes.

ALLERGENICALLY POTENT HOUSE DUST PRODUCED UNDER CERTAIN CLIMATIC CONDITIONS PRECIPITATES SYMPTOMS OF RESPIRATORY ALLERGY IN ALLERGIC PERSONS

In South Africa, Ordman[22] defined a group of respiratory allergy sufferers—the "Climate Group"—in whom symptoms appear at first glance to exemplify, *par excellence*, true climate-provoked allergy. Their symptoms are aggravated or indeed often initiated when they visit or live on the coast. On their return inland they experience an amelioration and even cessation of symptoms.

The climate differences between coast and inland have already been shown in a series of charts giving the climate pattern. In brief, at the coast there is a high relative humidity with a high temperature, both in narrow range, during the day and throughout the year, whereas in inland regions these have a wide range, and the patient thus escapes an almost constantly humid and warm environment. Ordman[23] has also prepared charts showing the climate patterns of other countries including Brazil, Argentina, Israel, Spain, Portugal, Holland and parts of the United States of America where there is a remarkable similarity of differences between the coastal and inland climates with those already described for South Africa. In these countries, there are also "Climate Group" respiratory allergy patients whose symptoms

TABLE I. COMPARISON OF SKIN TEST REACTIONS WITH VARIOUS DILUTIONS OF STANDARD PURIFIED ANTIGENS OF COASTAL AND INLAND HOUSE DUSTS

Patient	Standard Purified Antigen			Patient	Standard Purified Antigen		
	Dilution	Coastal	Inland		Dilution	Coastal	Inland
Van R.	1/100,000	+++±	±	Gol.	1/100,000	++	+±
	1/10,000		+±		1/10,000	+++±	+±
	1/1,000		+++		1/1,000		+++±
de W.	1/100,000	+++±	+±	du P.	1/100,000	++	−
	1/10,000		+±		1/10,000	+++±	±
	1/1,000		+++		1/1,000		++±
Kot.	1/100,000	+++±	−	Wki.	1/100,000	+±	−
	1/10,000		−		1/10,000	+±	−
	1/1,000		++±		1/1,000	+++	++
Bla.	1/100,000	++	−	Ste.	1/100,000	+++	+±
	1/10,000	++±	±		1/10,000		+++
	1/1,000	+++±	+		1/1,000		
Law.	1/100,000	++±	−	Sch.	1/100,000	++	±
	1/10,000	+++±	±		1/10,000	++±	±
	1/1,000		+		1/1,000	+++±	++

are worse at the coast. The basic climate requirement for the existence of the "Climate Group" of patients is thus constant high humidity in narrow range and, certainly in warmer countries, constant high temperature. In these patients, no consistent factor other than "climate" was originally found to explain the contrasting symptoms at the coast and inland. Detailed information has already been given[23] exonerating pollens, air-borne fungi and other exogenous allergens of the etiology. The most striking finding in the study of respiratory allergy in South Africa over the years is that the "Climate Group" of respiratory allergy sufferers shows a high degree of skin-sensitivity to house dust. This led to an inquiry as to whether house dust derived from the coast is more allergenically potent than that from inland regions. Experimental investigations have already been described[23] of the skin-testing of 123 patients which showed that coastal house dust was without doubt more allergenic than that from inland sources. Confirmation of this point has more recently been obtained with the co-operation of Dr. H. D. Barnes of this Institute. Standard purified antigens have been prepared from both coastal and inland house dusts by the method of Rimington and Maunsell.[24] Table I shows a series of ten house-dust-sensitive patients in whom skin tests were carried out with dilutions of these antigens purified in identical manner from coastal and inland house dusts. The strikingly greater potency of coastal house dust antigen is again evident.

Other workers have also found that respiratory symptoms became worse under humid conditions with house dust as the aggravating factor. Thus, Vallery-Radot[25] observed the frequency of house dust allergy in persons living in houses built along the banks of the Seine, and he and his co-workers[27] later referred to house-dust asthma as the most frequent form of asthma in France and in Europe. Ten Cate[28] stated that allergy to house dust was one of the main causes of asthma and rhinitis attacks in the Nether-

lands. Van Geuns[29] has shown that eighteen of thirty-five asthma patients, who were from the low-flying regions of Holland and were practically free from asthma while living in the high mountains of Davos in Switzerland, developed asthmatic symptoms when allowed to inhale Dutch house dust. He showed also, by means of intracutaneous skin tests with specific extracts from house dust collected in these two regions, that house dust from Holland was stronger than that from Davos.

As a result of his investigations on this subject, Ordman[23] deduced the universal principle that the "Climate Group" of respiratory allergy patients is associated etiologically with a basic climate pattern (constant high humidity, with, especially in warm countries, constant high temperature, both in narrow range), together with a high degree of sensitivity to house dust. If this concept is true, then quite clearly "climate" as such is not directly responsible for symptoms in this group of sufferers, but symptoms are due to the specific effect of allergenically potent house dust in persons sensitized thereto. In other words, in the so-called "Climate Group" of respiratory allergy patients, it is a different type of house dust and not climate at all that gives rise to symptoms at the coast.

It is interesting to speculate on the reasons for the greater allergenicity of coastal house dust. Rimington,[30] Maunsell[31] and Harsh[32] have postulated that in damp atmospheres bacteria and molds grow and develop more prolifically, and it is by their biological action on the local house dust that the latter becomes a more potent allergen. This seemed a plausible hypothesis and worthy of consideration. Davis,[33] however, investigating the effect of mold colonies upon the allergenic potency of house dust, concluded that the hypothesis of increase under humid conditions of the skin-reactive material in house dust by the developmental activity of molds was untenable. On the contrary, the evidence suggested that molds utilized dust allergen(s) in their metabolism. But nearly twenty-five years ago Cohen, Nelson and Reinerz[34] pointed out that in their experiments house dust allergen developed in cotton linters under conditions which excluded the possibility of contamination with other common allergens. Its formation was not dependent on bacterial or mold action on the linters. They came to the conclusion that the allergen developed during the "aging" process of the linters and probably also of feathers, kapok and other substances.

There is, however, another aspect which deserves attention and relates to the potency of house dust from different regional sources. It may be that house dust, in general, has fundamentally the same allergenic value but that its potency *diminishes* under certain circumstances, for example on exposure to solar radiation or to atmospheric ionization.

Solar radiation consists of ultraviolet light directly from the sun as well as ultraviolet light from the sky. The total solar radiation thus emitted is reduced on its way through the atmosphere, and the degree of reduction depends upon the geographical situation, the altitude above sea level and on the cloudiness and turbidity of the atmosphere. Riemerschmid[35] carried out

a solar radiation survey in 1937-38 in South Africa and showed that there was a greater ultraviolet radiation all the year around in the inland as compared with the coastal regions. Durban and Johannesburg are at the same latitude, but the solar radiation readings at Bloemfontein inland were always greater than those at the coastal city of Durban; the number of bright sunshine hours being 9.1 and 5.8 respectively. The difference is explained by the greater amount of cloud at the coast, the thicker layer of atmosphere above the sea as compared with that of the highveld inland, and the influence of smoke and carbon particles in the area of Durban town and harbor in contrast to the clear air of the observing station at Bloemfontein.

The above findings suggest that Johannesburg and other inland house dusts, subjected as they are to the action of a greater amount of ultraviolet light possibly associated with the effects of ionization, *lose* allergenic potency. This, then, provides an alternative explanation of the diminished potency of inland house dust. The question must be considered, however, whether such radiation (whatever its effect in the open) would penetrate into the interior of dwellings to influence the house dust there. It is of significance in this connection that recent work reported by Buettner[20] indicates a very close relationship between parallel indoor and outdoor measurements and thus obviously ions and probably also their space charges diffuse quickly into normal houses. Natural charges of ions may, therefore, be capable of affecting people indoors.

Investigations are in progress in our laboratories where coastal house dust is exposed to the influence of sunlight and other forms of irradiation for varying periods of time to find whether the potency will thereby be diminished or otherwise altered.

It is tempting to consider another possibility to account for the coastal aggravation of symptoms described above, viz., a direct effect of *atmospheric ionization* on the respiratory allergy sufferer. Information, however, is not available with regard to the qualitative and quantitative aspects of ionization in South Africa, and it is thus not yet possible to make any deductions about such an hypothesis. The general implications of an atmospheric ionization factor in respiratory allergy are considered in the following pages.

ATMOSPHERIC IONIZATION—A FACTOR IN RESPIRATORY ALLERGY

There is considerable evidence that atmospheric ionization is of significance in human well-being and especially in respiratory allergy.

Ions in the atmosphere owe their origin in nature to cosmic rays and radioactive particles in the air derived mainly from the disintegration of radioactive substances in the Earth's crust. Other sources of ionization are thunderstorms and winds. Ions are also generated from the action of ultra-violet light as well as artificially from x-rays, high-frequency current apparatus and radioactive substances. It may be that the state of

atmospheric ionization at any given time is that unifying factor previously mentioned which could explain the anomalous experiences of physicians in regard to "climate" and respiratory symptoms in their allergic patients. In other words, it seems likely that symptoms are provoked by the quantity and quality of the co-existing atmospheric ions rather than by the obvious gross weather changes of temperature, humidity, barometric pressure, et cetera.

Biological Effect of Ionized Air and Its Influence on the Health of Man.— There is hardly any question of the fundamental importance of ionized air which acts at cellular level. Chase and Willey,[36] in view of the contradictory results previously reported, carried out experiments on inbred cultures of wild-type *Drosophilia melanogaster* in ionized air under various conditions. They noted the resulting coloration and subsequent death of the larvae in twenty-four to forty-eight hours and thus confirmed the ability of ionized air to affect living material. Holloway,[37] studying the growth and weight of the glands of rats, found strong indications that air ions influenced adrenocortical activity with some cyclical pattern.

There is much suggestive evidence which indicates that atmospheric ionization might explain disease occurrence or disease forebodings in man.

Dessauer[38] showed that ionization of the atmosphere had biological effects on normal subjects and on patients with various diseases of the respiratory system. Chizhevsky[39] concluded from his experimental work that the inhalation of ionized air regulated the electrical properties of the blood.

Kopaczewski[40] stated that changes in the electricity of the atmosphere frequently associated with a fall in temperature and increased humidity of the air had a bad influence on bronchial asthma. Petersen[41] reported that the asthmatic patient responded to cyclonic alterations irrespective of the fact that the immediate environmental temperature and humidity remained uniform. He thought also that there was a marked increase in asthmatic deaths during times of change in the cyclonic front when the barometric pressure dropped.

It is common for sufferers from "rheumatism" to declare that they are affected by the weather and that they are able, by their symptoms, to predict weather change. It has often been observed that asthmatic patients could foretell the coming of a storm by the aggravation of their symptoms. Brown[42] studying the relationship of atmospheric conditions to reactions from various illnesses, stated that in Iceland, rheumatic and arthritic attacks were associated with the Aurora Borealis.

Buettner[20] expressed the feeling of most students of climate and health in his remark that the complex of weather illnesses which could not be explained by thermal, hygric, chemical, aerosol, micro-organisms or similar environmental factors was more enigmatic than ever and thought that the trivial surface weather elements such as pressure, temperature and humidity were not the likely causes. He hinted that the successful treatment

of hay fever with artificially negatively-charged air might give a clue to the explanation of weather effect. Recent discussions on bioclimatology and the human organism reported by Alemany-Vall[43] related to studies on the influence of cosmic rays and the origin of magnetic storms and ionization disturbances; the biological and psychological reactions of individuals to cyclones; the occurrence of changes of ionization in the initial periods of major atmospheric disturbances predictable by metereo-sensitive individuals and the injurious effects of positive ionization in allergic diseases.

Significance of Polarity of Ionization.—Evidence has accumulated which shows that the polarity of the atmospheric ionization is of biological significance. In general, positive ionization is harmful to health but the presence of negative ions is beneficial and favorably stimulating to the physical and psychological states in man.

Brandan[44] has shown that variation in polarity in air ionization is quite able to produce some effect on the blood. He stated that a positive charge carried by the air might influence the cations Ca and K of the blood also positively charged and be concerned with contraction of the bronchial muscle. It could help neutralize the charge of the hydrogen ions and swing the pH towards alkalinity locally. It could also neutralize the charge of the stable electrons with negative sign of the colloids of the serum and favor their flocculation, which produces a more conducive medium for the absorption of allergens.

Okada[46] showed that the blood-sugar level in rabbits decreased with negative and increased with positive ionization. He also observed an increase in gastric acidity in persons exposed to negatively-ionized air and a decrease with positive ionization.

Danforth,[47] investigating the effect of air ions on the growth of chicks, found an increase in the rate of growth under negative ionization as compared with those under positive ionization or with controls. Worden[48] showed that mold spores in the atmosphere were reduced to 5 per cent of the normal concentration when the air was negatively ionized, and also found[49] that negatively-charged atmospheres exerted a stimulating influence on the growth and relative weight of certain organs of the golden hamster. He found that hamsters kept in negatively-ionized air developed an elevated blood pH with a significant increase in the CO_2-combining power of the plasma.[50] Rinfret and Wexler[51] found that, on exposure of animals to an atmosphere containing an excess of positive ions, there were changes in the adrenal glands. Histological examination indicated elaboration by the glands of both salt and carbohydrate-regulating corticoids. Nielsen and Harper[52] demonstrated that after four hours in a negatively ionized atmosphere, the succinoxidase content of the adrenal glands of rats showed a slight rise. The succinoxidase content was significantly reduced in positively ionized air for a similar period.

Krueger and Smith,[53] investigating the effect of air ions in the living mammalian trachea, found that animals exposed to high mobility positive

air ions administered by means of a tracheotomy aperture, displayed decreased ciliary activity, a decline in the mucus flow rate, contraction of the membranes of the posterior wall and an increase of vulnerability to trauma of the cilia and mucosal blood vessels. Similar treatment with negative ions reversed these effects and, if continued, raised the ciliary rate and often the mucus flow rate above their initial levels.

Dessauer[38] demonstrated substantial effects on man treated with artificial large ions and showed that while negative ionization was beneficial, positive ions were detrimental to health. Yaglou and co-workers[54] reported irritation of the nasal membranes as a result of positive air ion action. Kimura and co-workers[55] thought that comfort was dependent, in part, upon the polarity and the degree of ionization of the atmosphere. Hansell[56] found that negatively ionized air produced physical, mental and emotional uplift with comfort, exhilaration, friendly attitude, good temper and relief from hay fever and asthma. Positively ionized air produced directly opposite effects with fatigue, headaches, dizziness, nausea and faintness. Murphy,[57] emphasizing the value to health of negative ionization, pointed out that in mechanically-ventilated air-conditioned spaces there was an excess of positive ions and suggested that the ion balance might be the "missing link" differentiating man-made and nature's "fresh air." He noted that an excess of negative ions had been observed at certain famous spas, possibly accounting for their reputation as health resorts.

Erban[58] studied a group of test persons who inhaled positively ionized air for two months at three times a week for one hour. Negatively ionized air was inhaled during the second part of the experiment. He found that with positive ionization there was an increase in blood pressure, the albumins decreased and the globulins increased in the blood, the total and free chlorides fell and the 17-Ketosteroids increased. Negative ionization had no effect on the blood pressure, but there was an increase of albumins and a decrease of globulins.

It is not an uncommon experience of many physicians that asthmatic symptoms are alleviated at high altitudes, and the reasons given for this improvement generally referred to the absence of the more common inhalant allergens at high points. The question of atmospheric ionization, however, should be considered in this frame of reference. Klotz and Bernstein[17] suggested that at high altitudes in the decreased air pressure and lower humidity there was better ventilation and decrease in the amount of pollens, fungi and bacteria. Feinberg[15] similarly explained the immediate relief from wheezing or rhinitis which occurred in patients ascending in a plane to 7,000-8,000 feet as being probably due to the diminution in the air-borne allergens there. Hurst,[59] on the other hand, noted that at least 90 per cent of asthmatic patients lost nearly all their symptoms within a very short period after residence at a height of over 4,000 feet, but he thought the explanation did not lie solely in the relative absence of specific allergens.

Koller,[60] in his studies of the biological effects of the ionization of the atmosphere, showed that the number of ions in the air increased with increasing elevation and that the inhalation of negative ions was the same as inhaling the air in mountain climates. Behounek and Kletcha[61] also believed that mountain climate was always characterized by a greater ionization than that of the low lands. Klotz and Bernstein[17] stated that the negative ions predominated on mountain tops but that positive ions increased with the approach of a thunderstorm. They speculated also whether asthmatic persons would respond better in a negatively charged atmosphere.

Ionization and Respiratory Allergy.—In regard to the influence of ionization on respiratory allergy conditions, various workers have already made comment for more than a decade.

Bierman[62] declared that negative ionization was of value in the treatment of a sinusitis and vasomotor rhinitis. Landsman[63] stated that the effects of weather changes and climate on asthma were due to changes in the ionization of the air and reported that sixty-four of seventy-nine asthma patients improved on the inhalation of air with a high negative ion content. Bulatov[64] described improvement in a large proportion of asthmatics treated with negative ionization. Murphy[57] stated that patients who used negative air ion generators reported favorable effects on hay fever and asthma, sinusitis and hypertension. Kornblueh and Griffin[65] reported that of twenty-seven hospital patients exposed to negative ionization in an experimental room, most of those with hay fever and asthma responded favorably. Repetition of the exposure during the ensuing season continued to show gratifying clinical results. Hicks[66] stated that from his personal experience and from empirical evidence, he knew of the therapeutic usefulness of negative air ionization, particularly on respiratory illness including asthma and hay fever. Shukalova and Pavluk[67] reported improvement in a large proportion of asthmatic patients treated with negative ionization. Winsor and Beckett[69] described the result of their studies indicating that positive and negative ions produced opposite biological effects. Positive ions give rise to irritation of the respiratory tract, especially when the humidity was low, the patient grounded and high ion densities employed. Kornblueh and co-workers[70] exposed 123 patients suffering from hay fever to positive and negative ionization. Favorable responses were elicited by the negative polarity, whereas positive ionization caused no relief or even increased distress. The beneficial effects of negative ionization, however, were only temporary, as symptoms returned shortly after the patients were put back to their normal environments. These workers admitted that the mode of action of air ions was not well understood, but suggested a direct physiological action on the respiratory tract.

Vasilyev[71] recently has advanced the following interesting hypothesis to explain the mechanism of the effect of atmospheric ions on health. Air ions act upon the organism primarily through the lungs in the process of

respiration. Milliards of electric charges carried by the gas or liquid particles penetrate with every breath into the respiratory organs and reach the alveoli of the lungs where, depending upon the nature of the electric charge, they either excite or inhibit the sensory nerve-endings of the lungs. From here, the stimulating or inhibiting nervous impulses pass to the centers of the medulla oblongata and then to the higher departments of the central nervous system. Vasilyev also visualized the existence of an "electro-humoral" mechanism. This mechanism involved the penetration of air ions through the wall of the pulmonary alveoli into the blood which helped their electric charges to pass to the body cells. In turn, these cells carry negative charges on their surfaces. He thought that, with the aging of the organism and in disease, the magnitude of these charges decreased and accounted for the beneficial effects of the inhalation of negative air ions.

SUMMARY

The relation of climate and respiratory allergy is discussed and the literature quoted to show that, while it is generally acknowledged that climate has an effect on respiratory allergy, there is little agreement as to the factors involved. No acceptable explanation nor any basic principles have so far emerged scientifically to connect climate and respiratory allergy.

Three possibilities are considered regarding the way in which climate might affect respiratory allergy:

1. Climate or climate change acts as an *irritant* and like any other irritant, is able to provoke symptoms in a basically allergic person.

2. Under certain specified climate conditions the local *house dust* is rendered more allergenic. The susceptible patient is therefore affected not directly by the climate itself but indirectly by the allergenically potent house dust.

3. "Climate" effect on the allergic patient is due not to gross climate factors like temperature, humidity, barometric pressure, et cetera, but to the *atmospheric ionization,* qualitative and quantitative, existing in his environment at the time.

The possibility is considered that atmospheric ionization is the unifying factor reconciling the widely differing views and experiences of physicians in regard to the effect of particular climates on respiratory allergy.

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South African Institute for Medical Research
Hospital Street
P.O. Box 1038
Johannesburg, South Africa

EFFECT OF THE MOTHER ON GOAL SETTING BEHAVIOR OF THE ASTHMATIC CHILD

ROBERT P. MORRIS, Ph.D.
Boston, Massachusetts

A FUNDAMENTAL postulate in current psychosomatic theory is that many illnesses result partly from physiological effects of, or responses to, chronic, characteristic emotional tensions in the person who is affected. A second postulate is that the child's early relationship with his mother is crucial in the development of such tensions. The point at which theories diverge is the matter of degree of specificity that can be attributed to these tensions—to what extent specific conflicts are associated with specific illnesses.

A number of writers, for example Ludwig[13] and Deutsch,[6] believe that there are no specific emotional tensions or conflicts predisposing to given diseases. Franz Alexander, on the other hand, maintains that there are specific emotional conflicts that predispose to specific psychosomatic illnesses. It is this theoretical position, applied to bronchial asthma, that the present study examined.

Of asthma, Alexander says, "The psychological component in bronchial asthma represents a retreat from action into a dependent, help-seeking attitude . . . Likewise the nuclear conflict in asthma cases is well-circumscribed and distinct: fear of separation from the mother or her substitute."[3]

Alexander sees the specific emotional conflict in asthma in the context of a characteristic relationship between the mother and the asthmatic child. The mother rejects her child, asking that he achieve independence at an early age, and not depend on her. The child longs for dependence and protection, fears further rejection, hence suppresses the open dependency of crying, and the forbidden sexual impulses which also threaten separation. Alexander suggests several ways in which allergy might then enter the picture, with the final resultant of the bronchial asthma syndrome.[7]

DEVELOPMENT OF HYPOTHESES

From Alexander's writings, and from the observations and experiments of a number of others, notably French, Mohr, Gerard and Ross,[7] Miller and Baruch,[14,15,16] Treuting and Ripley,[18] Jessner,[9] Abramson,[1,2] and Coolidge,[5] it is apparent that a distinctive kind of relationship between the asthmatic child and his mother can be delineated. The mother is said to be unconsciously rejecting her child, while being consciously overprotective and controlling. She is over-ambitious for him, and wants him to become an achieving little adult very early to gratify her own, usually narcissistic,

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Professor Morris is currently affiliated with Boston University and with the Brockton Veterans Administration Hospital.

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needs. The child has his normal need for nurturance greatly increased by the mother's frustrating controls. He becomes angry, but is unable to express this anger for fear of losing the gratifications he has. The mother keeps him dependent, and pushes him to accomplish excessively at one and the same time. He wants to grow and to be independent, but he needs his mother's protection, because he has never been given enough to satisfy his early dependent needs.

The child partially resolves this conflict by developing a hostile-dependent relationship with the mother and conforming, as well as he can, to her conscious wishes. This resolution fulfills one object of the conflict—it gains a kind of independence, and it keeps a minimum of mother's protection. An attack of asthma occurs when this defensive structure threatens to break down. The child's asthmatic attack represents a suppressed attempt at fulfilling the other object of the conflict, symbiosis with the mother, by crying out for her.

It was possible to derive testable hypotheses from this theory. Since the child tries to conform to the mother's wishes, he allows her to exert influence on a specific set of ego functions. He permits the mother to interpret reality for him by shaping his behavior to a greater extent than would be so in a normal mother-child relationship.

Furthermore, the theory implied that, for the mother, a crucial part of reality is that of the child's ability to achieve. We saw that she perceives this in a specific way. She is over-ambitious for the child and so perceives his ability to achieve as higher than it actually is. She communicates this judgment of reality to the child; he attempts to conform by setting his goals correspondingly high.

This was a testable consequence of the theory. One other premise was necessary before formulating hypotheses which could be tested experimentally. That premise was that a child's relationship to reality is still developing during latency. As support for this premise there were data both from psychoanalytic investigations and from descriptive studies such as that of Gesell.[8] Both sources indicate that latency is a period of increased and developing attention to reality.

Hypotheses.—At this point, it was possible to formulate two hypotheses. (1) Asthmatic child-mother pairs behave more like one another with respect to goal setting than do nonasthmatic child-mother pairs. (2) Asthmatic children's levels of goal setting rise when the mother is present and participates in the activity.

Predictions.—Three predictions were formulated by which to test these hypotheses. (1) The presence and participation of mothers of asthmatic children in goal setting tasks will result in more similar goal achievement behavior among asthmatic children than among non-asthmatic children. (2) Asthmatic children's levels of goal setting will be higher when their

mothers are present and participating in a goal setting task than when the children perform the task alone. (3) The difference in level of goal setting of asthmatic children from an "alone" situation to a situation where their mothers are present and participating in the goal setting will be greater in a positive direction than the corresponding difference for nonasthmatic children.

METHODOLOGY

General Considerations.—A technique was available that was peculiarly adapted to the study of goal setting behavior: the level of aspiration technique. This technique is a test of goal-setting behavior in which a person is given a task to perform, usually consisting of a series of trials, with a range of possible scores for each trial. After he performs each trial, he is asked what he expects to get on the next trial, and so on, through a given series. The measure which is most often used as the index of goal setting behavior or "level of aspiration" is the discrepancy between each performance and the succeeding estimate of performance on the next trial. This technique has been extensively investigated and used both with adults and with children, including asthmatic children.[10]

In 1951, Little and Cohen[11] administered a dart-board aspiration task to asthmatic children from age four to twelve, with the children's mothers present and independently estimating the child's performance in each trial. Their procedure was to ask the mother to write her guess as to the child's next performance on a score sheet, prior to the child's spoken guess. Then the child performed on the trial. He was told his score and whether he succeeded or failed. Interaction between mother and child was not controlled or dealt with systematically. The mothers could and did make comments to the children about their performance. With this procedure, the authors found that both the mothers and their children had significantly higher levels of aspiration than did a control group composed of nonasthmatic patients, their siblings and their mothers.

It was the reasoning of the present study that the presence of the mothers was the crucial variable in the production of high levels of aspiration in the asthmatic children. With this point of view, one would expect latency age asthmatic children to have significantly higher levels of aspiration when their mothers were present than when they were absent. The present methodology allowed examination of this point.

In a subsequent publication, Cohen[4] reported a replication of the 1951 Little and Cohen experiment. He found no difference between asthmatic and nonasthmatic groups with respect to level of aspiration. It was the reasoning of the present study that the lack of systematic control over the type and purpose of interaction between mother and child led to inconsistent results between the replication and the original study. By this reasoning, if a particular kind of interaction with an explicit purpose is specified for the mother and child, the results would be consistent and predictable. The

present methodology allowed examination of this point. The details of this methodology are presented below.

Apparatus.—The instrument used to measure level of aspiration was the Rotter Aspiration Board.[17] The procedure is to roll a steel ball along a grooved board, aiming at a series of holes bored at three-fourths inch intervals at the other end. These holes are numbered from one through ten to one in such fashion that the center hole is highest in value and the holes decline in value as they get more distant from the center hole. The task set for the subject is to try and get the highest score possible in whatever series of trials is given.

Subjects.—Subjects were drawn from the population of clients of the pediatric out-patient department of The Boston City Hospital, its allergy out-patient department, and the allergy out-patient department of the Boston Dispensary. Both hospitals are general medical and surgical hospitals which serve almost exclusively people of lower to lower-middle socio-economic status.

The experimental group consisted of twenty unselected, consecutively admitted asthmatic children between the ages of five and ten, and the mothers of these children. Twelve of these children were diagnosed as having pollen and perennial asthma, five as having perennial asthma, and three as suffering from pollen asthma. Eleven had additional allergic disorders.

The control group consisted of twenty unselected, consecutively admitted children who were being treated at the Boston City Hospital for a variety of non-asthmatic and non-allergic complaints, and the mothers of these children. At the time of the study none of the children had asthma, nor did they have a history of asthma.

There were no significant differences between the experimental and control groups with respect to age, intelligence, or stated education of either parent. The average age of both groups was 7.7 years; the average intelligence* of the groups was 94.1 and 92.7 respectively; the reported parental education was 10.3 and 10.7 grades, respectively.

Procedure.—Each child was seen alone by the experimenter who administered a series of five practice trials and eleven experimental trials with the Rotter Aspiration Board. In instructing the child, the experimenter made the following four points: (1) This is a test of your ability and judgment. (2) The idea is always to aim for the ten; to get as high a score as possible. (3) Before you start each time, however, I want you to tell me what score you expect to get. (4) Then you should try to get as high a score as possible; that is, aim at the ten. By aiming high, you have the best chance of hitting what you guess, or better.

*Intelligence was estimated from the Vocabulary and Block Design subtests of the Wechsler Bellevue Intelligence Scale for Children.

Each child was also given the same number of trials with the mother present and participating in the goal setting. The same instructions were given in this situation, with the additional information that the experimenters were also interested in how her child worked with another person on this task. The mother was told that for the next fifteen trials she and her child should agree on the guess as to what the child was going to get on each shot.

In order to control for the possibility of changes in performance or levels of aspiration as a function of habituation with the task, the experimenters used four orders of presentation. Five subjects in each group were tested in each of the four orders:

1. Intelligence measure—Alone—Together
2. Alone—Intelligence measure—Together
3. Together—Alone—Intelligence measure
4. Together—Intelligence measure—Alone

For each child under each condition ("Alone" and "Together"), there were ten discrepancy scores—the differences between each performance on a given trial and the estimate of what the next performance would be. The mean of these ten discrepancy scores was, operationally, the level of aspiration measure.

TABLE I. THE VARIANCES OF THE CHANGES IN LEVEL OF ASPIRATION FROM ONE SITUATION TO THE OTHER FOR BOTH GROUPS

	Asthma Group Variance	Nonasthma Group Variance	F	P
Changes from "Alone" to "With mother"	1.0299	2.5375	2.46	.05

RESULTS

The results supported the two general hypotheses of the study.

The first prediction was that the presence and participation of the asthmatic children's mothers in the goal setting would have effects on the level of aspiration more similar to one another than the effects of the mothers on nonasthmatic children. In terms of operations, this meant that the variance of the distribution of changes in level of aspiration from the "alone" situation to the situation "with mother" would be smaller for the asthmatic group than for the nonasthmatic group. A test of the difference between these two variances yielded an F or 2.46, with the nonasthmatic variance being the greater. This value of F, for 19 and 19 degrees of freedom is significant beyond the .05 level of probability. The first prediction was therefore confirmed. The findings for this prediction are summarized in Table I.

The second prediction was that the asthmatic group's level of aspiration would be higher with the mother present and participating than when she was not present. A test of the difference between the mean level of aspiration when the mother was not present and the mean level when she was present produced a "t" of 4.447. This value is significant beyond the .001 level of probability for 38 degrees of freedom. The second prediction was therefore confirmed. The findings for this prediction are summarized in Table II.

TABLE II. THE LEVEL OF ASPIRATION OF THE ASTHMATIC CHILDREN WHEN THEY WERE ALONE, AND WHEN THEY WERE WITH THEIR MOTHERS

	Ave.	S.D.
Alone	−0.010	1.045
With mother	+1.155	0.899
t_{38}	4.447	
p	.001	

The third prediction dealt directly with the change of the level of aspiration of the asthmatics from the "alone" situation to the situation with the mother present in relation to the corresponding change in the nonasthmatic group. The prediction was that the change would be greater in a positive direction for the asthmatics than for the nonasthmatics. A test of the difference between the mean change for the asthmatic group from the alone to the together situation and the corresponding mean for the nonasthmatic group produced a "t" of 2.240. This value is significant beyond the 0.2 level for 38 degrees of freedom. The third prediction was therefore confirmed. The findings for this prediction are summarized in Table III.

TABLE III. LEVEL OF ASPIRATION CHANGES OF ASTHMATIC AND CONTROL GROUPS FROM THE "ALONE" SITUATION TO THE "WITH MOTHER" SITUATION

Asthma		Control			
Ave.	S.D.	Ave.	S.D.	t_{38}	p
+1.165	1.015	+0.195	1.593	2.240	.02

One additional substantive finding appeared. On inspection, it appeared that the level of aspiration of the asthmatic group in the "alone" situation was significantly lower than that of the nonasthmatic group. The mean level of aspiration of the asthmatic group in the "alone" situation was −0.010, with a S.D. of 1.045. The mean level of aspiration of the nonasthmatic group in the "alone" situation was +0.895, with a S.D. of 1.785. A two-tail test of the difference between these two means produced a "t" of 1.901. This value has a probability of approximately .06 for 38 degrees of

freedom. Although this does not quite reach the conventional significance level of .05, the finding indicates that in the "alone" situation the levels of aspiration of the asthmatic patients strongly tended to be lower than those of the nonasthmatic patients.

There were two artifacts which might have had some influence on the results of the study. The first was the possible differences between groups and between experimental conditions in performance or actual achievement on the task. We discovered that the findings were not influenced by differences in performance or actual achievement on the task. There were no significant differences and no reliable trend. Performance scores averaged 5.8 with a range of 5.7 to 5.9, regardless of group or experimental condition.

The second artifact was the possible differences between groups and between experimental conditions due to habituation with the task. Here also there were no significant differences. There were no changes in performance or level of aspiration due to habituation with the task.

Thus the findings of the study were not attributable to these two experimental artifacts. Each of the three predictions was confirmed and both hypotheses were supported.

DISCUSSION

The present study used an experimental approach and methodology in the field of research on psychological factors in bronchial asthma. The most important and perhaps the most numerous of the previous studies have been clinical descriptions of the asthmatic personality. The original monograph by French and Alexander[7] led to other investigations oriented primarily towards psychiatric interviews of varying depths with asthmatic adults[18] and occasionally with the mothers of asthmatic children.[16] Sometimes the presence of the mother was more or less systematically varied[9] in relation to observations of her effect on the asthmatic child. Occasionally, these observations were supplemented by interviews with both the mother and the child.[5,9]

While these studies expanded and clarified the French and Alexander findings, the objection that continually arose was that the findings were not specific to asthma. The child's dependence on the mother, the mother's rejection of the child screened by her attitude of overprotection, the subsequent hostile-dependent relationship were considered by many authors to be characteristic of other diseases in addition to asthma. Specificity-nonspecificity itself became a controversial theoretical issue.[3,12] In an effort to resolve this theoretical dilemma, different approaches to the phenomena were tried. The present study was an attempted different approach, an experimental approach, although one not primarily focused on the specificity dilemma.

The findings of the present study supported the hypothesis that asthmatic children and their mothers relate in a characteristic way with respect to at least one aspect of their relationship—the child's goal setting.

One of the two major findings indicated that this aspect of the relationship is consistent. That finding was the greater homogeneity of changes in the level of aspiration in the asthmatic group. Asthmatic child-mother pairs behave significantly more like one another than do the nonasthmatic child-mother pairs. We concluded that goal setting is an area of functioning that is handled more consistently among asthmatic children and their mothers than among the general population of nonasthmatic children and their mothers. A regular, consistent phenomenon is in operation.

The nature of this phenomenon was made explicit by the other major finding. That finding was that while the mothers of the nonasthmatic children have no consistent effect on their children's levels of aspiration, the mothers of the asthmatic children do have a consistent effect on their children. When these mothers are present and participating, the child's level of aspiration rises. We concluded that the asthmatic child is dependent upon the mother for help with a specific kind of reality testing (the assessment of his ability to achieve), and the mother influences this assessment consistently in an upward direction.

Given these results and conclusions, however, it is possible to argue that the consistent rise in level of aspiration is attributable to the support afforded to the child by the presence of the mother, rather than to the impact of her high aspirations for her child. The statistical data did not permit a definitive choice between these two alternatives, but behavioral observations gave some clues. Although in some cases there was an open struggle over how high the goal should be set, more frequently it was the mother who set the goal, with the child passively agreeing. Usually, there was a good deal of warmth and understanding apparent between mother and child. This kind of behavior was more consistent with the interpretation that the mother imposes her assessment of achievement reality, and the child accepts this assessment without challenging with his own.

There are several theoretical points that these observations corroborate. The children's acceptance of higher verbal goals in the absence of higher performance supports French's conclusion that, for the asthmatic child, maintaining protective contact with the mother through verbal means is of great importance. The absence of a struggle against the mother's high standards suggests that the anger against the mother's controlling forces is repressed. Such anger might be turned inward, as Miller and Baruch have suggested. Finally, the result of these psychic maneuvers is an apparent excessive closeness between the mother and the child. They often act as one in the decision of what the child can achieve. This relationship might truly be called symbiotic, as were the relationships Jessner and Cooldige observed between asthmatic children and their mothers; the relationship which we observed was certainly a very close one.

A comparison of the present study with that done by Little and Cohen provides further clarification. Little and Cohen found (when both the mother and the asthmatic child were present but independently setting goals

for the child) that both the mother and the child had significantly higher levels of aspiration than did control mothers and children. The present study indicated that asthmatic children, when alone, tend to have lower levels of aspiration than nonasthmatic, and that the presence and participation of the mother raises the asthmatic children's levels to those of the nonasthmatic. These findings emphasize that the asthmatic child's achievement is a function of the mother's setting the standards higher than the child does. The resultant of forces from mother and child around the child's level of goal setting is equal to the level to which the nonasthmatic child aspires with or without his mother's influence. One could speculate, still following the same theoretical lines as above, that neither party has really satisfied his own needs with this result.

One final aspect of the findings of the present study is the sharp delineation of the asthmatic child's situation. In this relationship with his mother, the typical asthmatic child of latency age is almost completely unable to aspire unless his mother is present to tell him how and how much. One can speculate that on passing through the latency stage, the asthmatic child completes the process of internalizing the mother's standards and integrating them into the rest of his reality-testing functioning. Thereafter, his mother's needs for his having high goals in addition to his own reluctance to aspire, become relatively permanent aspects of his personality. This also implies that the mother's influence has tremendous importance in the asthmatic child's development of self-esteem, or in his development of any kind of confident self-image.

The research process does not actually end at this point. In respect to clarifying further the nature of the asthmatic child-mother relationship in addition to its specificity to asthma, the experimenter is faced with several questions.

1. Are there other aspects which form a consistent part of the relationship? In other words, are there other ego functions that the mother influences in a characteristic way? Other kinds of stimuli, perhaps projective material, might be used within the same general experimental design to determine the consistency of the mother's influence in other life areas. The theory suggests separation and independence as areas of importance in asthma.

2. Within a given family is the asthmatic child the only child that has such a relationship with his mother? An experimental design with the siblings of asthmatic children as controls would be a direct method of determining this.

3. Is the dependent-overprotective relationship (or any aspect of it) necessarily specific to the disease of asthma? The present study was not designed to answer this question, but to provide a first step towards an answer. It was proposed that some aspects of the relationship might be specific to asthma. It was then demonstrated that a certain kind of be-

havior could differentiate asthmatic child-mother pairs for a general population of nonasthmatic pairs. The next logical step is to determine whether an asthmatic group will differ in the same consistent way from groups of children who suffer with other psychosomatic illnesses. The specificity theory states that there are consistent differences in the mother-child relationships in different psychosomatic disorders. A comparison of different psychosomatic mother-child pairs on this aspect of their relationship would be a possible partial test of that theory.

SUMMARY AND CONCLUSIONS

This study was a partial test of the hypothesis that there is a specific kind of relationship between asthmatic children and their mothers. The central postulate of this study was that the mothers of asthmatic children are overly concerned with the control of these children and over-ambitious for them. These children, in turn, are overly dependent and conforming, particularly in the area of achievement. There were two hypotheses: (1) asthmatic child-mother pairs behave more like one another with respect to goal setting than nonasthmatic child-mother pairs, and (2) the asthmatic child's level of goal setting rises when the mother is present and participating in the goal setting.

These hypotheses were tested by means of a modified level of aspiration procedure. Twenty asthmatic children of latency age and twenty controls were given the Rotter Aspiration Board task. One series of trials was administered when each child was alone with the experimenter and one series was given when the child's mother was present and participating in the goal setting activity.

The results supported both hypotheses and justified the conclusions that (1) goal setting is an area of functioning that is handled more consistently, in the same way, among asthmatic children and their mothers than among the general population of nonasthmatic children and their mothers, and (2) the asthmatic child is dependent upon the mother for help with a specific kind of reality testing—the assessment of his ability to achieve—and the mother influences this assessment consistently in an upward direction. Finally, some additional avenues of research were suggested to clarify further the nature of the asthmatic child-mother relationship. Some approaches to the question of specificity of this relationship to asthma were also suggested.

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143 Bedford Street

ERROR IN PSYCHIATRY

A second error arises from the universal and naïve reaction of *post hoc ergo propter hoc*. I label this error as the worship of the great god Coincidence. It is difficult, impossible in fact, for untutored man to discriminate between coincidence and cause. It is easy to say when a man has been disappointed and then raves in mania, that the disappointment causes his disease; just as it is pleasant to do something, whether it is to pray, give electricity, remove tonsils, and to ascribe the recovery of the patient to prayer, electricity, and tonsillectomy. We cannot rest without cause; unless we are mathematically inclined and know about probability, chance, and error, we ascribe the striking event that is antecedent to the illness or the recovery to the series of events that follow. The disposition to praise and blame thus enters largely into the acceptance of coincidence as cause.—ABRAHAM MYERSON, *The Story of Human Error*, Joseph Jastrow, Editor, New York, Appleton-Century, 1936.

REDUCTION OF MAINTENANCE DOSES OF PREDNISOLONE IN BRONCHIAL ASTHMA BY THE CONCURRENT USE OF HYDROXYZINE

MILTON M. HARTMAN, M.D., F.A.C.A.
San Francisco, California

WHILE ELIMINATION of the cause, or proper desensitization therapy, constitutes the ideal treatment for asthma of extrinsic origin, symptomatic or adjuvant treatment is often necessary. This requirement is even more frequent in the less numerous cases from the intrinsic group. Prednisolone has been an effective synthetic gluco-corticoid (anti-inflammatory steroid) for such symptomatic relief,[3,8,12,22] and has definite advantages over the naturally occurring cortisone and hydrocortisone. It is four or five times more potent on a weight basis and occasions less sodium retention and potassium loss in therapeutically equivalent doses. A minority of cases, usually in the higher dosage levels, respond to prednisolone and not to the original gluco-corticoids.[32] However, the use of any available anti-inflammatory steroids in high enough dosage and for enough time, causes one or more manifestations of Cushing's syndrome.[24] We are only uncommonly dealing with replacement therapy. The incidence of the more serious complications of gluco-corticoid therapy, such as peptic ulcers,[6,17,18] activated or re-activated tuberculosis,[33] or osteoporosis,[15,21] is roughly proportional to the dosage level and duration of treatment. Dosage must therefore be kept to a minimum consistent with acceptable relief[24] and long-term therapy not lightly undertaken. It seemed advisable to explore methods of reducing the gluco-corticoid requirements of asthma patients necessitating such therapy.

The majority of conditions for which gluco-corticoids are prescribed are associated with emotional stress. A large percentage of illnesses, organic at their inception, add anxiety factors as they become more severe and incapacitating. The deprivation of oxygen is a threat to life and security, and the individual with unrelieved asthma is understandably beset by fear and anxiety. The latter intensify the bronchoconstriction and mucosal edema, leading to a vicious cycle.

The importance of emotional conflicts in bronchial asthma, allergic dermatoses, and other allied conditions has been stressed by many authors. The excellent 1943 summary by Brown and Goitein[7] listed so many known

From the Allergy Clinic and Department of Medicine, Stanford University School of Medicine, San Francisco, California.
Dr. Hartman is Assistant Clinical Professor of Medicine, Stanford University School of Medicine, Stanford, California.
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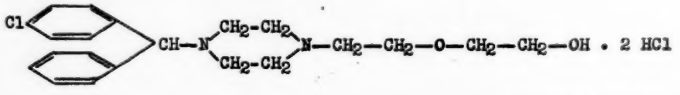
and varied psychologic factors related to the etiology of asthma that one should be cautious about accepting restrictive theories. Miller and Baruch[26] champion the "maternal rejection" theory, plausible in children but frequently difficult to apply in adult life. Abramson[2] approves this approach but adds the corollary of a "mutual engulfment" between parent and child before the rejection, real or fancied. It is commonly held that psychosomatic symptoms represent a discharge via the autonomic nervous system of psychic energy which is repressed or blocked from acting in its normal channels. In the case of asthma, this discharge affects the bronchial tree. Modern workers conjecture that the consequences of these emotional reactions will result whether or not the patient is aware of the disturbing stimulus.[23]

Asthma may result from the physiologic consequences of chronic aversive affective drive states. Anxiety or fear is probably the most common and important aversive affective state.[23] When the individual is unable to diminish anxiety, either because the reality of the situation precludes the possibility or because of inadequate or deteriorated psychologic defenses, asthma may result—particularly in a constitutionally-predisposed individual. A tranquilizing or ataractic agent might be a useful adjuvant to prednisolone—not only to control tension, fear and anxiety—but to counteract the overstimulation that gluco-corticoids cause in a minority of patients.[27]

Abramson[1] recommended the judicious use of chloral hydrate, acetyl carbromal, and the barbiturates in asthma, particularly when anxiety and hostility were factors. He also pointed out that then-current antihistaminic drugs often had hypnotic effects, which might or might not be desirable. The use of the more recent "tranquilizing" agents in a variety of allergic disorders was reported by Eisenberg,[14] who found that 32.2 per cent of his patients were helped by chlorpromazine, 21 per cent by reserpine, and 38.5 per cent by meprobamate. Santos and Unger[29] tried hydroxyzine in an assortment of allergic diseases and controlled or improved all patients except those with allergic rhinitis. Nervousness was controlled in the latter condition, but the authors noted no objective improvement. The thirty-two patients with asthma all showed improvement and a dosage schedule of 10 to 25 mg hydroxyzine three or four times daily was followed.

Structurally, hydroxyzine appeared to be the most logical agent for allaying tension and anxiety. It is classified as a psychotherapeutic antihistaminic,[11] having the requisite "ethylamine key" in its structure,[19] and an ether-linkage contributing to its sedative action. Its appreciable antihistaminic action and slight anticholinergic[20] action are assets in the treatment of allergy. No adverse effects upon bronchial secretion have been noted. The formula for hydroxyzine hydrochloride is:



Hydroxyzine has been useful in the treatment of emotionally disturbed adults,[13,30] hyperkinetic children,[5] senile anxiety,[30] and dermatoses affected by psychogenic stimuli.[28] There are no significant side effects except occasional mild and transient drowsiness. Effective doses have ranged from 5 mg to 125 mg daily. By using hydroxyzine-prednisolone combination, Tillis[31] and Warter[32] were able to reduce the prednisolone maintenance requirements significantly in half of their patients afflicted with rheumatoid arthritis. Brown and Seideman[8] demonstrated the superiority of prednisolone to cortisone and hydrocortisone in patients with allergic disorders. The same investigators[9] stated that a combination of hydroxyzine and prednisolone was more effective than either given separately but did not indicate the actual extent to which the gluco-corticoid dosage could be reduced. One hundred sixteen cases of bronchial asthma were studied, thirty-four treated with hydroxyzine-prednisolone combination, thirty-six on prednisolone alone, twenty-three on hydroxyzine alone, and twenty-three on placebos. Standard daily doses of 20 mg prednisolone and 40 mg hydroxyzine, or 20 mg hydroxyzine alone, were used on alternate weeks, using a double-blind system.

Arbesman and Ehrenreich[4] conducted a longer term single-blind study on fifty-eight allergy patients and used prednisolone and prednisolone combined with hydroxyzine. Of their forty-nine cases of bronchial asthma, fourteen patients claimed that they felt better using the combination, but only three were as well on a slightly lower dosage of steroid. Relief of tension, pruritus, and insomnia were the beneficial effects ascribed to hydroxyzine. Forty-four of their fifty-eight patients were kept comfortable on 10 mg or less of prednisolone daily.

Fox[16] conducted a double-blind short-term study on thirty-three patients, thirteen of them asthmatic, on prednisolone alone; and thirty-four patients, fifteen of them asthmatics, on a prednisolone-hydroxyzine combination. In the latter fifteen asthmatic cases, ten obtained excellent and five obtained good results. In the thirteen asthmatic patients on prednisolone alone, six were classified as excellent and four as good. In only twelve of the sixty-seven patients could alternate trials be made. Fox used initial daily doses of 10 to 20 mg prednisolone (divided) and initial daily doses of 20 mg to 40 mg of hydroxyzine. It was stated that an effort was made to reduce the initial dosage to the minimum that would produce adequate results. The actual minima obtained, however, were not stated.

By using tablets combining 10 mg of hydroxyzine with 5 mg of prednisolone, Santos and Unger[29] were able to relieve three patients suffering from bronchial asthma with half the usually recommended dose of steroid. The results were excellent and remained persistently satisfactory even when doses were decreased to one tablet daily.

The aforementioned studies of the 101 asthmatic patients who had been on a combined hydroxyzine-prednisolone regime did not settle the extent to which the prednisolone maintenance requirement could be reduced. Also

left unclear were the types of cases in which such dosage reductions could be effected. The study did not encompass enough cases on long-term therapy with unequivocally stabilized maintenance requirements. Only sixty-one patients acted as their own controls (first on prednisolone alone and then on the combination). Not enough patients underwent more than one pair of trials. Finally, there was insufficient information given as to the severity and etiology of the asthma. It is hoped that the present study will meet these objections.

The present investigation has two main purposes:

Purpose 1: To ascertain the actual extent to which the prednisolone maintenance requirements in various types of bronchial asthma can be reduced by the concurrent administration of hydroxyzine.

Purpose 2: To compare the relative effectiveness of hydroxyzine, meprobamate, and phenobarbital for reducing such maintenance requirements. Phenobarbital was selected because it was representative of a group of compounds which have been standard sedatives for decades. Meprobamate is a widely-used tranquilizing agent of recent vintage.

METHODS, MEDICATIONS, CLINICAL MATERIAL, AND CRITERIA

The patients were on steroid medication for one or more of the following reasons: (1) complete intractability to other forms of treatment, (2) insufficient relief from other forms of treatment, (3) inability to cooperate on other methods of treatment, (4) previously started by other clinics or private physicians on gluco-corticoids and either unwilling or unable to relinquish them (the majority of these should never have been started on such medication), and (5) adverse side reactions to commonly employed medications.

The single-blind method was used because of the necessity of knowing the patient's state of medication at all times. The possibilities of sudden serious complications are always present in such a group, and one does not wish to introduce factors which may delay or complicate diagnosis. This was primarily a study of maintenance therapy rather than initial therapy. An important object was to keep the patient ambulatory no matter what his status was originally. The dose of prednisolone employed in each trial, alone or in combination, was sufficient to afford acceptable relief of symptoms. This meant essentially complete disappearance of symptoms in cases of mild and moderate severity. In severe cases it meant improvement to a point that permitted substantially normal activity. Objective signs were reduced markedly in all cases.

Two hundred and twenty-one patients were started on this project. Nineteen did not follow through sufficiently to warrant inclusion in the final analysis. Of the 202 remaining, fifty-nine or 29 per cent were eliminated from the final tabulation because it was impossible to determine a true prednisolone maintenance requirement. In these cases the need for

prednisolone was constantly fluctuating and at times disappeared. These fifty-nine included all of the known placebo reactors identified from previous studies on other drugs; their elimination left a group of 143 from whose reactions to medication valid conclusions could be drawn. Their ages ranged from twenty-one to sixty-seven.

One hundred forty-three patients, seventy-four male and sixty-nine female, entered into the final tabulations. Three basic questions had to be answered in each case:

1. Was the wheezing dyspnea seasonal or perennial?

2. Was the asthma predominantly of extrinsic or intrinsic origin? All patients had undergone skin tests, inhalation tests, or elimination diets. Some cases were admittedly difficult to categorize. Although there are obvious objections to this type of classification, it has the advantages of simplicity and universal recognition.

3. Were there significant emotional influences or conflicts present which could precipitate, aggravate, or prolong asthma? The patient often volunteered such information during the routine history-taking. At propitious occasions specific inquiry was directed toward family, social, sexual, educational, employment, business, and other personal situations which could produce mental stress. This type of questioning served not only to provide immediately useful information but to alert the patient to factors which he had not considered previously. In the majority of cases the necessary information for classification was obtained within the first five visits. In others, specific incidents over a period of time provided telltale clues to the patient's conscious or unconscious behavior.

In the opinion of the author, emotional factors, overt or unconscious, were considered significant if (1) they were definitely present and (2) if they effected a precipitation or intensification of symptoms not explainable on any other basis. These criteria are admittedly subjective. Since their application results in generalities, a subclassification of the emotional situations involved would serve no purpose and would needlessly complicate the following tables. Some comments, however, are pertinent at this point. In these adult patients the "maternal rejection"[2,10,26] theory was not as easy to apply as in child cases, but mother substitutes or images were frequently found. Frequently patients exhibited dependency, frustration, resentment, or repressed hostility, and gained relief from crying. On the whole, when emotional factors were significant, the end result was usually anxiety, conscious or unconscious. The author's observations tend to confirm those of Leigh,[25] that there is no specific psychologic constellation or common personality existing in asthmatic patients. The author also finds application in the field of asthma for the general "Uncompensated Affect Hypothesis" of Kaplan and Kaplan,[23] that any affective reaction evoked by any psychic stimulus may give rise to psychosomatic disease. The

psychosomatic symptom or intensification of symptoms of organic disease is the physiologic result of inadequate psychological defense.

According to the three basic headings, the cases were divided as follows:

Group 1.	21	Seasonal	21
	122	Perennial	122
Group 2.	88	Extrinsic	88
	55	Intrinsic	55
Group 3.	71	Significant Emotional Factors Present	71
	72	No Significant Emotional Factors Present (Ten of these later developed overt anxiety as a result of severe prolonged illness.)	72

Forty-six patients requiring 20 mg or more daily of prednisolone (as the sole medication) were classified as severe.

The tablets used for Purpose 1 were: Prednisolone 5 mg*; Prednisolone 5 mg and Hydroxyzine 10 mg combined.** Additional tablets used for Purpose 2 were: Phenobarbital 32 mg, Meprobamate 400 mg, and Hydroxyzine 10 mg.†

RESULTS OF TRIALS

Group 1: (Twenty-one Cases of Seasonal Extrinsic Asthma with No Significant Emotional Factors Present)

Eighteen of this group also had seasonal allergic rhinitis ("hay fever"). The cases were observed through two (grass) pollen seasons and were alternated every three weeks on tablets of prednisolone and prednisolone-hydroxyzine. There were no observable differences in the number of tablets required for maintenance of comfort. The number of cases at each dosage level of prednisolone follows:

4 cases—	5	mg every	6 hours	(20 mg daily)
9 cases—	5	mg every	8 hours	(15 mg daily)
5 cases—	5	mg every	12 hours	(10 mg daily)
3 cases—	2.5	mg every	12 hours	(5 mg daily)
21 cases				

The daily maintenance dosage of prednisolone for the group as a whole was 280 mg. The average daily dose was 13.3 mg.

Group 2: (Thirty Cases of Perennial Extrinsic Asthma with No Significant Emotional Factors Present)

The tablets of prednisolone and prednisolone-hydroxyzine were alternated every three or four weeks for periods of thirteen months to two years. No essential differences could be noted in the maintenance requirements. The number of cases at each dosage level of prednisolone follows:

Chas. Pfizer & Co., Inc., Brooklyn, New York, kindly furnished the following materials for this investigation:

*Sterane, brand of prednisolone.

**Ataraxoid, brand of prednisolone 5 mg and hydroxyzine 10 mg combined.

†Atarax, brand of hydroxyzine.

1 case	—5	mg every 4 hours	(30	mg daily)
3 cases	—5	mg every 6 hours	(20	mg daily)
8 cases	—5	mg every 8 hours	(15	mg daily)
7 cases	—5	mg every 12 hours	(10	mg daily)
4 cases	—2.5	mg every 8 hours	(7.5	mg daily)
4 cases	—2.5	mg every 12 hours	(5	mg daily)
3 cases	—2.5	mg on retiring	(2.5	mg daily)
30 cases				

The daily maintenance requirement for the group as a whole was 337.5 mg. The average daily prednisolone requirement was 11.2 mg.

Group 3: (Thirty-seven Cases of Perennial Extrinsic Asthma with Significant Emotional Factors Present)

Each case was alternated on tablets of prednisolone and prednisolone-hydroxyzine for periods of three to twelve weeks. Six cases underwent only one pair of comparison trials; the rest each had at least two pairs. The patients were under observation for periods ranging from thirteen weeks to two years.

Daily Prednisolone Requirement Under Prednisolone Alone		Daily Prednisolone Requirement of Same Cases on Changing to Prednisolone-Hydroxyzine Combination	
Cases	Dose	Cases	Dose
4	30 mg	0	30 mg
		1	20 mg
		1	15 mg
		2	10 mg
11	20 mg	0	20 mg
		9	15 mg
		2	10 mg
11	15 mg	2	15 mg
		7	10 mg
		2	7.5 mg
5	10 mg	0	10 mg
		2	7.5 mg
		3	5 mg
5	7.5 mg	1	7.5 mg
		2	5 mg
		2	2.5 mg
1	5 mg	0	5 mg
		1	2.5 mg
37 cases		37 cases	

The daily prednisolone maintenance requirement for the group as a whole was reduced from 587.5 mg to 380 mg and the daily average dose from 15.9 to 10.2 mg. This diminution amounted to 35.2 per cent. Thirty-four of the thirty-seven (92 per cent) were able to reduce their daily dose.

Group 4-A: (Eleven Cases of Perennial Intrinsic Asthma with no Significant Emotional Factors Present—Daily Dose of Prednisolone, 15 mg or below)

These were not classified as severe cases. Each one was alternated on tablets of prednisolone and prednisolone-hydroxyzine for periods of four to six weeks. Two cases only underwent one pair of comparison trials; the rest had two or more pairs. They were under observation from sixteen weeks to twenty-one months. There were no observable differences in the maintenance requirement of prednisolone. The number of cases at each dosage level of prednisolone follows:

3 cases—	5	mg every	8 hours	(15 mg daily)
4 cases—	5	mg every	12 hours	(10 mg daily)
3 cases—	2.5	mg every	8 hours	(7.5 mg daily)
1 case —	2.5	mg every	12 hours	(5 mg daily)
11 cases				

The daily maintenance dosage of prednisolone for the group as a whole was 112.5 mg. The average daily dose was 10.2 mg.

Group 4-B: (Ten Cases of Perennial Intrinsic Asthma with No Significant Emotional Factors Present—Daily Dose of Prednisolone Alone, 20 mg or above)

These were classified as severe cases; as time went on they all developed overt anxiety. Each patient was alternated on tablets of prednisolone and prednisolone-hydroxyzine for periods of three to eight weeks. Every case underwent two pairs of comparison trials. The patients were under observation for periods ranging from five months to nineteen months.

Daily Prednisolone Requirement Under Prednisolone Alone		Daily Prednisolone Requirement of Same Cases on Changing to Prednisolone-Hydroxyzine Combination	
Cases	Dose	Cases	Dose
3	60 mg	0	60 mg
		2	30 mg
		1	20 mg
3	30 mg	0	30 mg
		2	20 mg
		1	15 mg
4	20 mg	0	20 mg
		4	15 mg
10 cases		10 cases	

The daily prednisolone maintenance requirement for the group as a whole was reduced from 350 mg to 195 mg and the daily average dose from 35 mg to 19.5 mg, a diminution amounting to 44 per cent. All ten (100 per cent) of these severely ill patients were able to reduce their daily dose.

Group 5: (Thirty-four Cases of Perennial Intrinsic Asthma with Significant Emotional Factors Present)

Each patient was alternated on prednisolone and prednisolone-hydroxyzine combination for periods of three to six weeks. The cases all underwent two sets of comparisons and they were observed for periods ranging from six months to eighteen months.

Daily Prednisolone Requirement Under Prednisolone Alone		Daily Prednisolone Requirement of Same Cases on Changing to Prednisolone-Hydroxyzine Combination	
Cases	Dose	Cases	Dose
2	30 mg	0	30 mg
		1	20 mg
		1	15 mg
11	20 mg	0	20 mg
		10	15 mg
		1	10 mg
10	15 mg	0	15 mg
		9	10 mg
		1	7.5 mg
7	10 mg	0	10 mg
		4	7.5 mg
		3	5 mg
3	7.5 mg	0	7.5 mg
		3	5 mg
1	5 mg	1	5 mg
34 cases		34 cases	

The daily prednisolone maintenance requirement for the group as a whole was reduced from 527.5 mg to 357.5 mg and the daily average dose from 15.5 mg to 10.5 mg, a reduction of 32 per cent. Thirty-three of the thirty-four cases (97 per cent) were able to reduce their daily prednisolone requirement.

Group 6:

This group of twenty-two patients was composed of eight members of Group 3, six members of Group 4-B and eight members of Group 5 who consented to further trials for carrying out the second purpose of this study. Maintenance doses were determined on tablets of prednisolone alone for three or four weeks and then with the following drugs (not necessarily in succession): Phenobarbital, 32 mg after meals and before retiring; Meprobamate, 400 mg every eight hours; Hydroxyzine, 10 mg every eight hours. The eight-hour schedule was usually accomplished by medication on retiring, on arising, and in mid-afternoon. Each combination with prednisolone was given a three or four-week trial.

Prednisolone Dosage (Daily)	Given Alone	With Phenobarbital 32 mg qid	With Meprobamate 400 mg q8h	With Hydroxyzine 10 mg q8h
5 mg q 4h (30 mg)	3	1	1	0
5 mg q 6h (20 mg)	9	8	6	3
5 mg q 8h (15 mg)	6	10	9	7
5 mg q12h (10 mg)	2	1	4	7
2.5 mg q 8h (7.5 mg)	2	2	2	3
2.5 mg q12h (5 mg)	0	0	0	2
	22 cases	22 cases	22 cases	22 cases

The daily prednisolone maintenance requirement of the group as a whole was 395 mg on prednisolone alone, 365 mg when given with phenobarbital, 340 mg when given with meprobamate, and 267.5 mg when given with hydroxyzine. The concurrent use of hydroxyzine reduced the group requirement for prednisolone 32 per cent, meprobamate concurrently reduced it 14 per cent, and phenobarbital concurrently reduced it only 7.6 per cent.

CONCLUSIONS AND DISCUSSION

The lack of change in maintenance requirements of prednisolone by the addition of hydroxyzine in the twenty-one purely seasonal (extrinsic) asthma patients suggests that the anxiety factor associated with severe illness was not present. The probable explanation is either (1) the patient knew from previous experience that his symptoms would disappear on schedule, or (2) the patient had confidence in his physician's prediction and reassurance, in spite of the fact that seasonal cases requiring glucocorticoid therapy were apt to be fairly severe.

The fifty-five perennial intrinsic patients as a group required a higher average maintenance dose, 18 mg, than the sixty-seven perennial extrinsic

cases, 13.8 mg. By using hydroxyzine concurrently, the figures could be reduced to 12.1 mg and 10.7 mg, respectively. The 32.7 per cent reduction in the perennial intrinsic group and the 22.5 per cent reduction in the perennial extrinsic group are consistent with the known higher incidence of emotional factors in the former group.

When, however, the cases are properly considered from the standpoint of presence or absence of significant emotional factors, the usefulness of the hydroxyzine-prednisolone combination becomes more clearly evident. Such factors were present in the seventy-one persons making up Groups 3 and 5, and the hydroxyzine allowed the combined group daily prednisolone requirement to drop from 1,115 mg to 737.5 mg, a reduction of 33.8 per cent. The average daily dose was reduced from 15.7 mg to 10.3 mg. When emotional factors were not present, as in the sixty-two cases comprising Groups 1, 2, and 4-A, there was no change in the average 11.8 mg daily maintenance requirement. If the Group 1 seasonal cases are eliminated, the latter figure becomes 11 mg, an amount more nearly comparable to the 10.3 mg previously mentioned.

Group 4-B was distinctive in that psychogenic factors were not present initially, consciously or subconsciously, but overt anxiety did develop during the course of treatment as the patient recognized the severity and refractoriness of his illness. A 44 per cent reduction, from 35 mg to 19.5 mg, in the average daily requirement of prednisolone was attained by the combined medication. If the ten cases of Group 4-B are added to the seventy-one of Groups 3 and 5, the resulting eighty-one patients had a group daily maintenance requirement of 1465 mg on prednisolone alone, but only 932.5 mg on hydroxyzine-prednisolone combination. The average dose dropped from 18.1 mg to 11.5 mg, a 36.3 per cent reduction. This 11.5 mg figure, attained by the presumable pharmacologic control of emotional influences, is comparable to the 11.8 mg average requirement of the sixty-two individuals without significant emotional factors. It may very well represent a measure of basic "organic" asthmagenic factors.

The use of hydroxyzine allowed seventy-seven or 53.8 per cent of the 143 cases analyzed to lower their prednisolone maintenance requirement. In thirty-one out of thirty-eight patients in which significant emotional factors were present, initially or eventually, and in which the daily maintenance dose of prednisolone alone was 20 mg or more, hydroxyzine reduced the dose to 15 mg or less. This is particularly significant because the incidence of complications of prednisolone therapy rises sharply when daily dosage level of 15 mg is exceeded.

A comment might be made that with daily prednisolone doses of 5 mg or less, we do not know the actual effective gluco-corticoid intake. Such doses do not completely suppress anterior pituitary activity[24] and the patient's own adrenals contribute to a variable extent. However, only eight patients on prednisolone alone and fifteen patients on hydroxyzine-prednisolone combination, a total of twenty-three, fell into this category.

All of these twenty-three persons needed small doses, for they experienced exacerbations upon discontinuance of the medication.

One could also comment that in the fifteen cases taking 10 mg or less of hydroxyzine daily and in which the prednisolone requirement was reduced to 5 mg or less, the amount of hydroxyzine was insufficient for therapeutic effect. This is not valid, however, because the tranquilizing effect of hydroxyzine has been demonstrated on as little as 5 mg daily.

The superiority of hydroxyzine to meprobamate and phenobarbital for lowering prednisolone maintenance dosage may result from a different site of action in the brain. The other explanation is that the same site is more affected by hydroxyzine's chemical configuration.

SUMMARY

1. When significant conscious or unconscious emotional factors are present in asthmatic patients, the concurrent administration of hydroxyzine allows an appreciable lowering of prednisolone maintenance requirements.

2. Hydroxyzine is a desirable adjuvant for allaying the anxiety factor in prolonged severe asthma.

3. The use of hydroxyzine in indicated cases usually allows reduction of daily dosage of prednisolone to 15 mg or less, thus avoiding the range in which the more serious complications of gluco-corticoid medication are most frequent.

4. Hydroxyzine allows a lower prednisolone maintenance dose in indicated cases than either meprobamate or phenobarbital.

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450 Sutter Street

THE OPEN MIND

The open mind, the reliance on example and persuasion rather than on authority—these are the heritage of the centuries in which science has altered the face of the earth. Science can help in diverse ways in preserving and extending this heritage. Its very universality speaks across frontiers to make truth manifest in lands otherwise darkened; its material applications create the preconditions—in leisure, in education, in means of communication—for the converse of men with one another.—J. ROBERT OPPENHEIMER, Address to the Winners of the Annual Westinghouse Science Talent Search, Washington, D. C., 1950.

THE IMMUNOLOGIC RESPONSE OF GUINEA PIGS TO THE INTRODUCTION OF EMULSIFIED RADIOACTIVE ANTIGEN, III

A. R. AMELL, T. G. METCALF, L. W. SLANETZ
and
ETHAN ALLAN BROWN
M.R.C.S. (England); L.R.C.P. (London)

A PREVIOUS REPORT discussed the retention locally of injections of emulsified iodinated bovine gamma globulin at, and the spread from, the site of deposition as determined in guinea pigs.[1] In a second study,[2] we reported how we could by visual methods determine the movement of water-in-oil emulsions. This, the third communication, is concerned with a determination of the immunological response to such emulsified antigens.

EXPERIMENTAL DATA

The antigen used was bovine gamma globulin (BGG). It was, as previously reported, iodinated with I^{131}. The concentrations of the solutions used were 10 and 20 per cent respectively. The emulsions were prepared by means of a Brown Emulsor. The BGG in phosphate buffered solution (pH 7.0) was equal in volume to the mixture, 1:9 of mannide mono-oleate (Arlacel A) and mineral oil (Drakeol 6 VR). Emulsions were similarly prepared for the control experiments. These either contained no antigen or else radioactive potassium iodide (Iodine as I^{131}).

Twelve guinea pigs were injected subcutaneously with 0.1-0.2 ml of emulsified BGG for two separate experiments. Evidence of antibody formation was determined by the technique described by Korngold and his associates.[3] This technique, as will be recalled, depends on the retention of antigen by antibody at the site of the initial injection. BCG is injected, and after a suitable interval, the BGG-I^{131}.

For this particular study, Korngold's technique was modified, but only in the fact that the test animal received two injections of identical quantities of BGG-I^{131}. The second site of injection was sufficiently distant so that no interference of radioactivity from the first site could affect it.

The observations were controlled by the injection of radioactive potassium iodide (I as I^{131}) emulsions in previously BGG-treated as well as untreated animals.

Immediately after each injection, the amount of radioactivity at the site was measured by placing the animal over a well-type of scintillation counter

From the Departments of Chemistry and Bacteriology, University of New Hampshire, Durham, New Hampshire.
Dr. Brown is Director, Asthma Research Foundation, Boston, Massachusetts.

TABLE I. THE RETENTION OF BGG-I^{131} IN IMMUNIZED GUINEA PIGS ONE TO THREE WEEKS AFTER INJECTION WITH BGG

Test Animals	Test Site				Control Site			
	Initial Activity	Hours			Initial Activity	Hours		
		6[1]	12	24		6[1]	12	24
Guinea pig No. 1								
Radioisotope count*	111000	—	80000	43500	113000	—	81000	43000
Per cent activity retained			72	39			72	38
Guinea pig No. 2								
Radioisotope count	262000	—	118000	81000	178000	—	155000	67500
Per cent activity retained			68	31			87	38
Guinea pig No. 3								
Radioisotope count	32000	25000	—	10500	65000	57000	—	27900
Per cent activity retained		77		33		84		41
Guinea pig No. 4								
Radioisotope count	24000	22000	—	6950[2]	37000	35000	—	17200
Per cent activity retained		93		29		95		47
Guinea pig No. 5								
Radioisotope count	8700	6250	—	4440	26000	13300	—	8050
Per cent activity retained		72		51		51		31
Guinea pig No. 6								
Radioisotope count	10600	8400	—	7800	12500	8600	—	8000
Per cent activity retained		79		74		69		64

*Counts per minute.
[1]Number of hours following injection of BGG-I^{131}.
[2]Measurement subject to variation. Count given represents average of three separate counts.

(Nuclear Chicago, Model DS5-5) and a scaler (Nuclear Chicago, Model 181A). When the injection sites had been marked, reproducible routine measurements were easily obtained. The radioactivity was measured at intervals of twenty-four hours until it lessened to a small quantity of the known initial value.

Immediately before the injection of the emulsified BGG-I^{131}, blood was drawn from the animals and its antibody content was found, first by means of complement fixation and second by precipitation tests. The first test system was incubated overnight at 4° C and the antigen was used in quantities of 2-4 units and the complement in 2 units. For the second test system, the serum was not diluted, but serial dilutions of antigen were used. The tests were read first as ring tests, then after mixing and overnight incubation, as flocculation tests.

The first experiment demonstrated that after the initial injection of antigen, the amount of radioactivity at the test and at the control sites was the same after one week and also after two weeks. But, after three weeks, there was greater retention of radioactivity at the test site. This was not large but it was a consistent phenomenon. The actual counts are listed in the first table. But, by neither complement fixation nor precipitin tests could antibody levels be measured in any samples of serum drawn.

Because the retention of radioactivity at the site of injection as present at the end of three weeks was greater but not sufficiently high for antibody formation to be uncovered, the experiment was repeated. The intervals were changed from one, two and three weeks to one, three and six weeks.

From the second table it may be seen that the response at the end of one and at the end of three weeks is little changed. But, at the end of six

weeks, there is a consistent pattern at the test sites which indicates greater retention of radioactivity. The table lists the count for each minute at each site and the amount of radioactivity present in terms of the percentage of the initial values. Because the counts are corrected for decay of radioactive iodine activity and background radioactivity, comparison of the several counts is not complex.

TABLE II. THE RETENTION OF BGG-I^{131} IN IMMUNIZED GUINEA PIGS SIX WEEKS AFTER INJECTION WITH BGG

Test Animals	Test Site				Control Site			
	Initial Activity	Hours			Initial Activity	Hours		
		24[1]	48	72		24	48	72
Guinea pig No. 1								
Radioisotope count*	14000	6200	4900	3896	20000	7300	5000	3943
Per cent activity retained		48.0	41.5	36.0		39.0	29.5	25.6
Guinea pig No. 2								
Radioisotope count	24000	11350	7792	5695	22000	7000	3900	2384
Per cent activity retained		51.5	38.7	30.8		34.5	21.0	14.7
Control Animals								
BGG-I^{131}								
Guinea pig No. 1								
Radioisotope count	17300	4465	1729	1064	16600	4275	1601	926
Per cent activity retained		28.0	12.2	8.0		28.0	11.8	7.4
KI (I^{131})								
Guinea pig No. 2								
Radioisotope count	126000	10000	5000	4100	146000	10000	5000	3700
Per cent activity retained		8.7	4.7	4.2		7.4	4.1	3.3

*Counts per minute.
[1]Number of hours following injection of BGG-I^{131}.

It is clearly indicated by the data that retention of iodine not organically bound is minimal. The retention of organically bound iodine is greater, but the organically bound radioactive iodine incorporated in an emulsion is retained for a longer time at the site of the injection.

At the end of three weeks, a trace of antibody was discovered to be present in one animal by means of serological methods. With the lowest dilution of antigen used, 1:100, there was a faint precipitate. In no other animal could positive precipitation or complement fixation be discovered by presently used techniques.

DISCUSSION

The present study is one of a continuous series of investigations into the behaviour of a number of antigens injected in the form of emulsions into both man and animals. The basic consideration is the role of incomplete adjuvants in a heightened state of refractoriness in the syndromes at the moment labeled as allergic.

The findings of the present study demonstrate that more of the BGG-I^{131} is retained for longer times in immunized as compared to non-immunized animals, namely guinea pigs. Korngold and his group had reported this to be true of iodinated ovalbumin as injected into immunized as compared to non-immunized rabbits. In the immunized rabbit, the antibody produc-

tion was the cause of the increased retention of the injected antigen.

The present study goes beyond the studies cited because it demonstrates the retention at both the site of the injection and also at another site at which no injection had been given. The comparisons lead to two observations.

The site of the injections retains more antigen than do areas which are not the sites of injections. In addition, the area not injected but of an immunized animal retains more antigen than does a similar site of a control, non-immunized animal. Although the exact site of the formation of the antibody is not known, it is generally present in higher quantity at the site of the injection.

Because only one of the twelve immunized animals demonstrated serum antibody levels, we may not conclude that the increased retention results from a concentration of humoral antibody at the site of the injection.

Characteristic of the site of the injection was a small, sterile abscess. It might be suspected that this is inflammatory in nature and, therefore non-specifically retains antigen.[4,5] But, such non-specific retention cannot be demonstrated because organically bound and non-organically bound I^{131} are both eliminated more rapidly from the animals treated with non-antigen-bearing emulsions. In the absence of antibody, the greater persistance of organically bound I^{131} suggests a slower rate of diffusion from the point of deposition.

SUMMARY

When guinea pigs are injected with emulsified bovine gamma globulin, the subsequent injection of radioactive-iodinated bovine gamma globulin (BGG-I^{131}) is retained for longer periods of time as determined at intervals of one, three and six weeks after the date of the initial injection. The greatest amount occurs at the site of the initial injection, but smaller although significant quantities are retained at other areas which have not been the sites of injections. In treated animals, the retention is assumed to result from antibody formation.

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Department of Chemistry (Dr. Amell)
University of New Hampshire

ALLERGY AND INFECTION OF THE RESPIRATORY TRACT
Differential Diagnosis

BURTON M. RUDOLPH, M.D. and JACK A. RUDOLPH, M.D., F.A.C.A.
Miami Shores, Florida

ONE OF THE most common precipitating factors of an asthmatic attack at any age is an acute respiratory infection. This fact, in the minds of many physicians, is responsible for the belief that infection is the principal cause of the asthma.[7] If one carefully studies the clinical and physiopathologic findings of allergic individuals who have frequent attacks of asthma, evidences of clinical or subclinical edema of the respiratory tract will be noted.[1] This edema becomes clinically obvious immediately upon exposure to a specific antigen. The presence of an edematous mucous membrane and the ischemia which results increases the susceptibility to infection. Infection in an allergic individual with such tissue usually results in a paroxysm of asthma. Immediate treatment of the infection is essential, but the improvement of the asthmatic attack should not lead to the conclusion that the infection is the primary cause of the asthma.

Prevention of chronic asthma and its complications can come from a complete study of the individual patient, the history, examination, laboratory tests and a thorough search for the causative allergens.[2] A remission from the asthma will result with the correction of physical defects, removal of the responsible allergens and hyposensitization.[3] In a few patients the infectious agent may be the primary cause of the asthma, but since our present knowledge of bacterial allergy is still incomplete, it would be hard to prove. In some individuals, what appears to be the onset of an acute respiratory infection, is merely a manifestation of an allergic reaction which involves the mucous membrane of the respiratory tract and is unrelated to an infectious agent, although the usual signs of respiratory tract infection and fever may be present.

In a paper presented before the pediatric section of the American Medical Association in June, 1931,[4] it was pointed out that

> "... Some of the conditions that are seen in children are those which are classified under the general heading of infections of the upper respiratory tract. Among them are included rhinitis, sinusitis, nasopharyngitis, pharyngitis, tonsillitis, laryngitis, tracheitis, and bronchitis. All these conditions may be infectious in origin, but are frequently manifestations of respiratory allergy, from which they must be differentiated if proper treatment is to be instituted. In addition, many of the true infections are complications of an underlying allergy and cannot be cleared up until the allergy predisposing the mucous membrane to infection is relieved."

Dr. Burton Rudolph is Instructor in Medicine and Dr. Jack Rudolph is Assistant Professor of Medicine, University of Miami School of Medicine.

TABLE I. HISTORY[4,9]

	Allergy		Infection		
	Seasonal	Perennial	Common Cold	Bacterial Cold	Adenoviral and Other Virus
Season	Yes	No	No	No	No
Other allergy	Yes	Yes	No	No	No
Allergy—family history	Yes	Yes	No	No	No
Etiology	Pollen	Food, dusts, molds, epidermals, and bacteria	? virus	Bacteria	Virus
Contagious	No	No	Yes	Yes	Yes
Attacks	Recurrent	Recurrent	Individual	Individual	Individual
Constitutional symptoms	Slight	Slight	Usually afebrile	Very severe	Severe
Local symptoms:					
Sneezing, wheezing	Very Severe	Severe	Slight or absent	Slight	Slight
Sore throats	Uncommon	Uncommon	Moderate	Very severe	Severe

Our experience has confirmed the fact that this knowledge is still not considered adequately unless the individual has typical hay fever or asthma.[5] Studies of the incidence of primary and recurring respiratory infections lose their real worth because allergic respiratory conditions are not separated from those which are infectious.[18,19]

Treating patients with upper and lower respiratory tract allergies inadequately or not at all, leads to intractable asthma and serious complications, such as chronic bronchitis, pulmonary emphysema and cor pulmonale. During the past thirty-two years during numerous interviews[6] with parents of asthmatic children, many stated that they were told that the child would outgrow the asthma, that there was no cure, that it was caused by infection, the emotions, or by a single antigen, dust. Following extensive medical and laboratory procedures, non-specific shock therapy, symptomatic treatment including steroids and the antibiotics, it is suggested that the patient take a trip to some location for a climatic or magic medical cure. When we see such patients later, the problem has become complicated; the patient is in extremely poor physical and emotional health and financially depleted, and as a result is usually not receptive to another medical evaluation and allergic treatment.[7]

Respiratory tract diseases which concern us in this paper may be divided into three classes: allergy, infection, and combined allergy and infection. The allergic diseases can be further subdivided into seasonal and perennial. The infectious diseases include the common cold, bacterial cold, adenoviral and other viral colds. These diseases can be differentiated by the history, physical examination, laboratory, and the results of treatment.

To consider allergy in relation to the problems of the respiratory tract is perhaps the most important point in the differentiation of infections.

In Table I we have listed the major points of difference between allergy and infection.

The history of these patients is of primary importance. The family history is positive in over half of the cases[8] and there are other allergic manifestations such as atopic eczema, angioedema, urticaria, asthma, hay fever, gastro-intestinal allergy, and allergic migraine either at the time of the examination or in the past history.[10] These conditions may be present if both allergy and infection exist at the same time but are absent in the purely infectious types. The studies on heredity in allergy, notably by Cooke and his associates,[8] reveal the importance of the family history. They pointed out that if both parents have allergy, 75 per cent of the offspring of such a union will develop an allergy by their tenth year. If one parent has allergy, approximately 50 per cent of the children develop some form of allergy by the end of their second decade. As a rule, if the family history is remote or difficult to ascertain, allergic symptoms will occur during or after the third decade.

Attacks due to allergy are usually recurrent when they are seasonal in nature; often they are perennial with mild symptoms between the attacks. They are not contagious and are not related to exposure to other cases. Usually the history will reveal frequent "colds" in the patient when other members of the family are free of these symptoms.

Attacks due to infection occur individually, since the infectious agents responsible confer a degree of immunity ranging from weeks to several months.[11] In the absence of complications they clear up completely without residual symptoms. They are definitely contagious and are related to exposure to other cases. Respiratory diseases of non-bacterial origin have been a perennial problem of all ages. The determination as to whether we are dealing with a common cold, bacterial, or viral infection often depends on long-term experience and judgment.

Patients with allergic rhinitis have such symptoms as itching of the eyes with lacrimation, itching of the nose with rhinorrhea, and itching of the nasopharynx and palate. These symptoms frequently are associated with bronchial manifestations evidenced by audible wheezing, cough, and expectoration. There may be itching of the skin on the front and back of the chest. It must be emphasized that other causes of wheezing such as foreign bodies, neoplastic disease, inhalation of definite respiratory irritants, and primary vascular disease of the lungs must be ruled out. In the case of the allergic patient there is often a definite history of an attack following exposure to an environmental dust, a household pet, or the ingestion of a food known to cause symptoms. The infectious cases rarely present these findings.

Attention to all factors considered will enable one to separate individuals with respiratory "colds" into proper categories. The examination and

laboratory studies make the differentiation more certain as enumerated in Table II. In the allergic patient the nasal mucosa appears pale, glistening, and edematous with a profuse serous discharge. The nasal blockage is due to swelling of the mucous membrane over the turbinates. The sputum is usually mucoid in character and a stained smear will show varying percentages of eosinophiles.[12]

TABLE II. EXAMINATION AND LABORATORY

	Allergy		Infection		
	Seasonal	Perennial	Common Cold	Bacterial Cold	Adenoviral and Other Virus
Conjunctival edema	Common	Common	Rare	Rare	Rare
Nasal excoriation	Rare	Rare	Usual	Usual	Usual
Nasal mucosa	Pale	Pale	Hyperemic	Hyperemic	Hyperemic
Nasal polypi	Rare	Frequent	No	Occasional	No
Nasal discharge	Serous	Serous	Serous	Seropurulent	Seropurulent
Sputum	Mucoid	Mucoid	Mucopurulent	Mucopurulent	Mucopurulent
Nasopharynx congestion	Slight	Slight	Moderate	Severe	Moderate
Cervical glands enlarged	No	No	Yes	Swollen and tender	Yes
Sinus involvement	No	Hyperplastic	No	Purulent	No
Wheezing breath sounds	Yes	Yes	No	Occasional	No
X-ray of chest: markings	No—early Increased—late	No—early Increase—late	No	Increased—Late in sino-bronchial synd.	No
Skin tests	Positive	Positive	Not reactive	Not reative	Not reactive
Leukocytosis	No	No	Slight	Moderate elevation	No
Eosinophilia: sputum and nasal	Yes	Yes	No	Occasional	No

In the infectious case, the mucous membrane is not too swollen, but appears hyperemic and irritated. The nasal discharge and sputum are usually seropurulent or mucopurulent with smears showing a predominance of neutrophils. Usually a high eosinophil percentage in smears from the nasal and bronchial secretion is diagnostic of allergy. Its absence or even a low count does not rule out an allergic diagnosis. Predominance of one cell type over another gives a clue as to the primary condition.

In addition to these more obvious signs, many allergic individuals show sinus involvement of a hyperplastic type; and usually in the perennial allergies polyps are frequently found.[12,15,16] These patients also reveal increased hilar bronchial markings on fluoroscopic examination and on x-ray films of the chest. Allergy testing by the use of the scratch, intradermal, mucous membrane, and passive transfer methods are strongly positive when good and potent antigens of a sufficient number are used.

The infectious cases, on the other hand, reveal purulent secretions, tenderness on pressure over the sinuses, and frequently frontal headaches and facial pain.[12,15,16] Bronchial markings are not increased with an individual common cold or viral cold, but may be increased in the long-standing bacterial sino-bronchial syndrome. Constitutional symptoms are usually pronounced and skin tests are negative.

TABLE III. TREATMENT

	Allergy		Infection		
	Seasonal	Perennial	Common Cold	Bacterial Cold	Adenoviral and Other Virus
Antihistamines	Of value	Of value	No	No	No
Sympathomimetics	Excellent	Excellent	No	No	No
Antibiotics	No	No	No	Excellent	No
Vaccines	No	Occasional value	No	Occasional value	Polyvalent-for 3, 4, and 7 type sero-adeno-virus
Cultures	No	No	No	Positive to specific bacteria	Virus isolated by tissue culture technique
Specific antigens: Avoidance followed by relief	Yes	Yes	No	No	No
Hyposensitization	Valuable	Valuable	No	Question-able	No
Steroid	Yes	Yes	No	No	No

Combined: Allergy and Infection
When allergy becomes secondarily infected, the most urgent of the conditions requires immediate care. Complete correction of the underlying allergy, however, is essential for complete remission of all symptoms.

After considering the history, the examination and laboratory studies, if one is unsure of the proper classification of allergy and if infection of the respiratory tract still exists, treatment as listed in Table III further assists in establishing the final diagnosis.[14,17] Nasal and bronchial symptoms of allergy are controlled by the sympathomimetic and steroid drugs to a high degree. Allergic nasal symptoms are benefited moderately by the anti-histamines. Prevention of allergic symptoms is accomplished by the avoidance of and hyposensitization to the offending antigens. Antibiotics and specific polyvalent sero types 3, 4, and 7 of the adenoviruses are excellent in most cases. Use of bacterial vaccines is of limited value in infection except in specific cases of proven sensitization.[13]

When there exists a combination of both allergy and infection of the respiratory tract, both require treatment. Control of the allergy is important for the relief of symptoms, the prevention of complications and even death.

SUMMARY AND CONCLUSIONS

The fact that temporary improvement results when antibiotic therapy is given does not necessarily indicate that infection is the cause of the allergy. Experience indicates that this is true only in a small percentage of children and adults. Removal of the primary etiologic allergens which maintain a state of partial swelling of the bronchioles may clear the clinical symptoms without the use of antibiotics. Failure to remove these allergens frequently results in chronic bronchitis, pulmonary emphysema with chest deformity, and *cor pulmonale*.

A diagnosis of allergy should be considered when the personal and family history is strong, when exertional expiratory wheezing recurs, and when relief

is obtained by the use of sympathomimetic drugs. These patients frequently demonstrate allergic stigmata of early childhood. Parents with such children are frequently told to wait, as the child may "outgrow" the condition. When these same patients come in for allergic study and treatment their symptoms have become constant with severe complications.

Differentiation of allergy and infection of the respiratory tract is tabulated. With a clearer understanding of the essential factors involved, proper allergic management can be given and good results may be obtained.

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9375 Park Drive

PHILOSOPHY

Philosophy is able to fancy anything different from what it is. It sees the familiar as if it were strange, and the strange as if it were familiar. It can take things up and lay them down again. Its mind is full of air and it plays around every subject. It rouses us from dogmatic slumber and breaks up our caked prejudices.—WILLIAM JAMES, 1842-1910.

STUDIES ON THE SENSITIZATION OF PATIENTS WITH BRONCHIAL ASTHMA TO THE VARIOUS POLLENS STUDY XI

Historical Document

I. CHANDLER WALKER, M.D.
Boston, Massachusetts

FOR A LONG TIME, it has been known that patients with bronchial asthma may be found to be sensitized to the various pollens and it is generally stated that sensitization to one pollen of a biological family means sensitization to all of the pollens of that family. The test for pollen sensitization is usually made only with dilutions of them. In our study on bronchial asthma we have found that sensitization to pollens does not always hold for the whole biological family, but that it is necessary to test with all the pollens belonging to that family. Furthermore, it is essential to use the whole pollen in the skin tests and if a positive reaction results the various dilutions of the pollen protein should be tested; if the dilutions alone are used many sensitized cases would be missed. Occasionally a patient who fails to give a skin reaction with the pollen of the plant will give a positive test with the leaves of that plant. The possibilities of sensitization to plants and to trees seem to be great.

While working on the methods of obtaining pollen from rag weed *(sic)* Wodehouse found that carbontetrachloride greatly facilitated the procedure and we have since found that this same method is applicable to all animophylous *(sic)* pollens. The flowers are collected just before they open and are then dried. The dry flowers are macerated with carbontetrachloride, pressed through gauze which allows the pollen and tetrachloride to escape; then the pollen is collected on filter paper. In a few hours the pollen on the filter paper becomes dry and can be removed as a fine powder; this is used for the tests. When leaves are to be tested, they are macerated while green in n/100 sodium hydroxide for several days, then pressed through gauze and the extract is slowly evaporated over a water bath to dryness. Either a gummy mass or a dry crust results and this is used for the skin tests. As we stated in the previous papers, a drop of n/10 sodium hydroxide is placed on the skin, cut with the pollen or the extract of leaves, as the case may be, in order to dissolve them.

Skin reactions with the pollens are usually clear-cut urticarial wheals of varying sizes and only occasionally does an erythema without a wheal result. In the type of definite reactions which they produce, the pollens closely resemble the alcoholic extracts of animal hair; these proteins give

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the largest reactions, probably because they are used in their original or natural state and have not been changed by manipulation in the preparation of their proteins as may be the case with the preparation of the food and the bacterial proteins.

The first part of the following description shows the relative frequency of reactions to the pollens of the Compositae family and the second part shows how the same patient may react to the different members of the same biological family.

TABLE I. THE SENSITIZATION OF PATIENTS WITH BRONCHIAL ASTHMA TO THE POLLENS OF THE COMPOSITAE FAMILY

Pollen	No. Patients Tested	No. Patients Positive	No. Patients Doubtful	No. Patients Negative
Ragweed (Ambrosia artemisifolia)	55	15	7	33
Goldenrod, (Solidago spi)	50	7	4	39
Daisy, white (Chrysanthemum leucanthemum)	25	5	3	17
Sunflower (Helianthus annuus)	7	3	4	3
Goldenglow (Rudbeckia laciniata)	6	3	0	3

Patient	Ragweed	Goldenrod	Goldenglow	Daisy	Sunflower
1	4+	+	3+	2+	+
2	0	0	0	2+	0
3	+	+	+	+	+
4	3+	±	+	2+	6+
5	4+	+		+	
6	3+	±			

In the first part of the table it is noted that in the same series of patients, twice as many are sensitive to rag weed as to goldenrod and that sensitization to the white daisy is very frequent. Since only those patients who were sensitive to both rag weed and goldenrod were tested with goldenglow and with sunflower we have a means of comparing the frequency of sensitization with each other and it is evident that the same patient does not give a positive skin reaction to all. The second part of the table illustrates the latter point better. One patient reacted positively to daisy and not with any other member of the Compositae group which was tried, two patients reacted very strongly with rag weed but only doubtfully with goldenrod. The fourth patient reacted very strongly with sunflower (6+), gave a good positive with daisy and rag weed, a single plus with goldenglow and a very doubtful reaction with goldenrod. Only one patient reacted equally strongly with all pollens. It must be borne in mind that the whole concentrated pollens were used in these tests, therefore if a dilution of the pollen had been used many of the pollens would not have reacted at all. Consequently it would seem advisable to test with all pollens of the Compositae family and to use the undiluted pollen.

In the same series of patients it is noted that more patients gave a positive reaction with timothy than with red top pollen and in a smaller number of

cases in the same series only one patient gave a positive reaction with orchard grass, but five were positive with corn pollen. The large number of positive and doubtful reactions with corn pollen make us suspect that some irritating substance may be present in the corn pollen. In the second part of the table it is noted that the first case was positive with timothy

TABLE II. THE SENSITIZATION OF PATIENTS WITH BRONCHIAL ASTHMA TO THE POLLENS OF THE GRAMINACEAE FAMILY

Pollen	No. Patients Tested	No. Patients Positive	No. Patients Doubtful	No. Patients Negative
Red top (Agrostis alba)	45	2	6	37
Timothy (Phleum pratense)	45	5	5	35
Orchard grass (Dactylis glomerata)	30	1	1	28
Corn (Zea mays)	30	5	6	19

Patient	Redtop	Timothy	Orchard Grass	Corn
1	±	2+	0	±
2	0	0	2+	2+
3	0	+	0	+
4	4+	4+	+	0
5	6+	4+	0	0

and only doubtful or negative with the other pollens in this family. In Cases 4 and 5, very strongly positive reactions (4+ and 6+) were given with red top and timothy, but both cases were negative with corn and only one reacted with orchard grass. The second case gave strongly positive reactions with orchard grass and with corn, but failed to react at all with red top and with timothy and the third case reacted a single plus with timothy

TABLE III. THE SENSITIZATION OF PATIENTS WITH BRONCHIAL ASTHMA TO THE POLLENS OF MISCELLANEOUS FAMILIES

Pollen	No. Patients Tested	No. Patients Positive	No. Patients Doubtful	No. Patients Negative
Rose (Rosa rugosa)	20	0	2	18
Clover, white (Trifolium incarnatum)	12	3	2	7
Lily, (Lilium superbum)	7	0	0	7
Pear, (Pyrus)	11	0	0	11
Maple, (Acer saccharinum)	9	0	0	9
Ash (Fraxinus nigra)	6	1	0	5
Willow (Salix spi)	20	2	0	18
Birch (Betula alnifolia)	6	0	0	6
Squash (Cucurbita maxima)	4	0	0	4
Sorrel (Rumex acetocella)	8	0	0	8
Buttercup (Ranuncular acris)	5	0	0	5
Pine (Pinus anstriaca)	5	1	0	5

and corn, but gave no reaction with orchard grass and red top. Again bearing in mind that whole pollen was used in these tests it would seem essential that the pollen of each of the widely-distributed members of the Graminaceae family should be used in the skin tests and that whole pollen should be used rather than a dilution of it.

Patients were not tested with the pollens presented in this protocol as a matter of routine; they were used only when there seemed to be a reason for it, such as the patient's history or the home surroundings would suggest. It is noted that clover, ash, pine, and willow did give positive skin reactions in an occasional case.

It is not necessary to give a table illustrating that the same patient may be sensitive to the pollens of widely-separated families since this fact is well known. This paper has already brought out the necessity of testing with the whole pollen; naturally before an attempt is made to desensitize the patient different dilutions of the pollen should be tested in order to determine the correct amount with which to begin desensitization. It is advisable to repeat at a later time all doubtful reactions and just previous to treatment they should be tested, since in the winter months cases may be negative to a particular pollen, but just before the season approaches the case may be positive.

Preparations of protein from the leaves of trees are used only in obscure cases and in those which seem to warrant it. One patient who had asthma only when at home and who reacted negatively with all of the pollens did give a positive reaction with poplar leaves and his house was surrounded with poplar trees. Another patient who reacted with willow leaves failed to react with willow pollen; this patient's house was surrounded with willow trees and treatment with willow pollen relieved all asthma. In obscure cases it would seem advisable to inspect the patient's surroundings and to make tests with extracts of the trees and other plants surrounding the home.

CONCLUSIONS

In determining the cause of seasonal asthma, the patient should be tested with the pollen of all of the common plants rather than with one plant from each family; the whole pollen should be used in these tests rather than a dilution of the pollen.

Occasionally it is advisable to test with the leaves of trees and other plants since patients may give a positive reaction with the leaves and not with the pollen of that same plant.

MAN AND NATURE

It is the exclusive property of man, to contemplate and to reason on the great book of nature. She gradually unfolds herself to him, who with patience and perseverance, will search into her misteries; and when the memory of the present and of past generations shall be entirely obliterated, he shall enjoy the high privilege of living in the minds of his successors, as he has been advanced in the dignity of his nature, by the labours of those who went before him.—LINNAEUS, *Systema Naturae*, tr. by W. Turton, 1806.

Progress in Allergy

PEDIATRIC ALLERGY

A Critical Review of the Literature

SHELDON C. SIEGEL, M.D., F.A.C.A. and
BAILEY J. LOVIN, JR., M.D.
Los Angeles, California

(Continued from the December issue)

DIFFERENTIAL DIAGNOSIS OF BRONCHIAL ASTHMA

In the differential diagnosis of bronchial asthma in children, fibrocystic disease must always be considered. With more refined diagnostic methods it has become apparent that the clinical features of this disease present an ever "widening picture," and there is not always a clear group of classic manifestations as has been thought in the past. In an excellent review of some of the present concepts in the diagnosis of cystic fibrosis of the pancreas, Barbero[212] discussed some of these clinical features and the screening tests which may be useful in making the diagnosis of this disease. He emphasized that the clinical features of pulmonary atelectasis, prolapse of the rectum, or biliary cirrhosis should immediately alert the physician to the diagnosis of this disease. Of particular interest to the allergist was his discussion of the screening tests. He pointed out that all of these tests are based on the elevated sodium chloride in the sweat or a marked deficiency of pancreatic enzymes in the duodenal fluid. The screening tests used for determining elevated chlorides in the sweat are founded upon the reaction of the chlorides with silver nitrate to form silver chloride which is visible on an indicator background. The one most frequently used is the Schwachman agar plate.[213,214] Webb and Geiger [215] as well as Knight *et al*[216] employed the same principle using a piece of filter paper saturated with 2 per cent silver nitrate solution. Gluck[217] described the use of a simple patch test, and in trials carried out in 207 patients demonstrated that it was accurate and reliable. (All the tests described have their limitations and are most meaningful as negative tests since a number of false positive reactions occur.) Gibson and Cooke[218] recently described a method of performing the test for chloride or sodium in the sweat of patients utilizing pilocarpine by iontophoresis. The authors claimed the method is reliable and has the advantage of being both rapid and painless.

Other tests utilized in the diagnosis of fibrocystic disease of the pancreas are based on techniques measuring the various deficiencies of pancreatic function. Frazier[219] in his discussion of the various methods of assaying pancreatic enzyme proteolytic activity pointed out that there are many difficulties encountered in the proper use of the gelatin-viscosity test. It was the author's opinion that for routine clinical diagnostic studies the Anderson-Early test is sufficiently accurate and the simplest test to use. Spector *et al*[220] presented a method for measuring the absorption of I^{131}-labeled fat which

provided a means of studying the lipolytic function of the pancreas and the efficacy of the addition of pancreatic extracts to the diet. Reemtsma *et al*[221] also reported on a similar type I^{131}-labeled fat and fatty acid absorption test.

The determination of sweat electrolytes improperly collected can be a dangerous procedure. Misch and Holden[222] reported the death due to heat stroke in a thirteen-months-old boy after he was subjected a second time to the Schwachman test for diagnosis of possible fibrocystic disease of the pancreas. The authors stressed the necessity of limiting the test to the thirty to ninety minutes originally recommended by Schwachman, depending on the rate of sweating and of frequent temperature recordings during the test period.

The concentration of electrolytes in the saliva, tears and duodenal contents in this disease have been studied by di Sant'Agnese *et al.*[223] Their studies showed a higher mean value of chloride in both the saliva and tears as compared to the controls. However, there was considerable overlap in the concentrations thus detracting seriously from the value of these determinations in the differentiation of cystic fibrosis from other diseases. Concentrations of chloride, sodium and potassium in duodenal fluid was found to be essentially the same in patients with cystic fibrosis as in the controls.

Recently two observations have been made which may limit the usefulness of sweat electrolyte determinations in differentiating fibrocystic disease from bronchial asthma. First, was the demonstration by Smoller and Hsia[224] in a study of thirty-eight families having children with cystic fibrosis of the pancreas that other members of the family are apparent carriers of the "fibrocystic disease gene" and have increased electrolytes in their sweat although not as elevated as those demonstrable in patients with clinical manifestations of the disease. Secondly, the demonstration by Hsia *et al*[225] that asthmatic children also have some abnormalities of their sweat electrolytes. By the Schwachman and Gahm plate method for determining sweat chlorides, it was found that sixty-eight of 123 allergic patients (55 per cent) showed a positive reaction. In contrast, only 128 of 1,001 persons in their control group (13 per cent) were positive. By conventional sweat determinations for sodium and chlorides, elevation of these electrolytes was also observed in the allergic subjects as compared to controls. This elevation of sweat electrolytes appeared to be unrelated to age, sex, race, types of allergy or the medications used by the patients. (The demonstration by these authors of elevated sweat electrolytes in allergic subjects should alert one not to make the diagnosis of fibrocystic disease on the basis of a laboratory test alone. However it should be emphasized that levels of sodium in the sweat above 50 to 80 meq per liter, depending upon the method, should be considered as highly suggestive of this disease.)

In a discussion of the pathogenesis of cystic fibrosis of the pancreas, di Sant'Agnese[226] postulated that perhaps a substantial number of children and adults with obstructive emphysema and other forms of chronic lung disease might belong to that group of individuals who are heterozygous carriers of the cystic fibrosis gene and in reality have "subclinical cases" of the disease. That this may actually be the case has been suggested by the findings of two different studies. Wood *et al*[227] studied the concentration of chloride in the sweat and the intestinal absorption of neutral fat and fatty acid in adults with chronic pulmonary emphysema and in children with fibrocystic disease of the pancreas. Five of the twenty-four patients with emphysema had abnormally high concentrations of chloride in the sweat, and four of these also had impaired absorption of neutral fat. The sweat chloride in the emphysematous subjects reverted to normal during severe salt restric-

tion. This pattern of response of the emphysematous subjects differed from that of children with cystic fibrosis of the pancreas, but was similar to that of the parents of these children. The authors concluded that some cases of chronic obstructive pulmonary emphysema in adults may represent *formes frustes* of fibrocystic disease of the pancreas. In the second study, Peterson[228] emphasized that cystic fibrosis is not exclusively a disease of children and should be considered among the possible causes of chronic endobronchial disease in adults.

TABLE I. INCREASED AERATION IN THE INFANT'S CHEST

I. Lung
  A. Obstructive
    1. One lung
      (a) Intraluminal—foreign body
      (b) Extraluminal—corynal cyst
    2. Regional
      (a) Pneumatoceles
      (b) Lobar emphysema
      (c) Congenital cystic disease
  B. Compensatory
    1. Whole lung
      (a) Bronchiolitis
    2. Regional
      (a) Intraluminal—secretions, atelectasis
      (b) Extraluminal—lymph nodes
II. Pleural Space
  A. Total
    1. Pyopneumothorax
  B. Regional
    1. Basal pneumothorax

Congenital abnormalities must always be considered in the differential diagnosis of asthma in infants and children. Sattler[229] described a case of congenital lobar emphysema in a two-months-old infant who had "heavy" breathing since birth. Treatment consisted of surgically removing the left upper lobe. The author reviewed the literature on this syndrome and discussed the differential diagnosis. It was stressed that a careful investigation will usually lead to the correct diagnosis and that these cases should be treated surgically.

Liebner[230] discussed some of the radiological aids that can be used in making the diagnosis of regional and generalized emphysema of the lungs in infants. He also presented a table of some of the conditions which will produce increased aeration in the infant's chest. (Surprisingly, the author neglected to include bronchial asthma in his outline.)

The different forms of cystic disease of the lungs were discussed by Quinlan et al.[231] They divided the varieties of cysts observed into four groups: (1) congenital, which included the bronchogenic and sequestral cysts, (2) the emphysematous cysts, the blebs and bullae, (3) the bronchiectatic cysts, and (4) the miscellaneous types of cystic changes such as hydatid. Campbell et al[232] reported their experience with five cases of congenital subglottic hemangioma and amplified their own experience by reviewing fourteen additional cases reported in the literature. The nineteen patients were all less than one year of age and twelve of them were girls. All showed evidence of laryngeal obstruction which was usually episodic and usually sufficiently severe to require tracheotomy. Detection of subglottic stenosis by roentgenographic, laryngoscopic or bronchoscopic examinations permitted clinical diagnosis to be made in eleven cases, permitting appropriate therapy in seven by roentgen or radium therapy or by surgical excision of the lesion. Twelve patients died: death resulted from asphyxia in eight cases that were undiagnosed or misdiagnosed clinically.

Bronchial obstruction due to an anomalous pulmonary artery has been

shown to be the cause of obstructive emphysema in infants by Sherman[233] and by Contro *et al.*[234] Clinical features of this anomaly include onset of respiratory difficulty in the neonatal period, prolonged expiratory phase with wheezing and right sided multilobular emphysema with mediastinal shift to the left. (It is, of course, important to recognize this anomaly since the condition can be corrected by surgery.)

Another congenital anomaly which can cause chronic and recurrent infection of the lung is interlobar bronchopulmonary sequestration. Two articles have appeared in the pediatric literature describing this condition.[235,236] That this congenital anomaly may remain quiescent for a prolonged period was demonstrated by Gallagher *et al*[237] who described two cases of interlobar bronchopulmonary sequestration of the lung in two young adults. One of these adult subjects had no trouble throughout his life, and the lesion was discovered by routine chest x-rays. The other subject revealed a history of an episode of pneumonia and presented an acute onset of hemoptysis, cough, dyspnea and foul-smelling sputum. These authors also reviewed the literature on this syndrome.

Buenaventura and Unger's[238] case report illustrated that a foreign body must always be considered in the differential diagnosis of bronchial asthma. These authors reported a three-year-old girl who presented a history and physical findings strongly suggestive of bronchial asthma. Because of failure to respond to the usual allergic management, other causes of the wheezing were sought. During the course of the child's illness, a progressive atelectasis of the right middle lobe developed. While being bronchoscoped, the child coughed up a vegetable foreign body which was thought to be a peanut and shortly thereafter the child became asymptomatic. The authors rightfully emphasized the fact that vegetable foreign bodies can produce bilateral wheezing and stressed the dangers of the inhalation by young children of foreign bodies, particularly peanuts. Miller *et al*[239] also emphasized that a foreign body in the bronchus should always be considered in children when there is acute or chronic lung disease even though a history of possible foreign body cannot be obtained and stressed that special care should be taken not to be misled by an asymptomatic interval. Johnson and Unger[240] reported a case of intractable asthma caused by aspiration of a cork from a nebulizer.

Although thoracic tumors are rare in children, they occasionally must be considered in the differential diagnosis of bronchial asthma. Richards and Reeves[241] present a classification of the mediastinal tumors and cysts that are found in children.

I. Superior mediastinal masses
   A. Cystic hygroma
   B. Cavernous hemangioma
   C. Thymic hyperplasia
   D. Dermoids and teratomas
   E. Lymphomas

II. Anterior mediastinal masses
   A. Dermoids and teratomas
   B. Pericardial cysts
   C. Thymomas
   D. Lipomas

III. Middle mediastinum
   A. Sarcoidosis
   B. Dermoids and teratomas
   C. Lymphomas
   D. Tbc

IV. Post mediastinum
   A. Alimentary cysts
   B. Neurogenic tumors
   C. Intrathoracic meningocele
   D. Bronchogenic cyst

A primary fibrosarcoma of the lung was reported in a two-year-old child by Gerbasi, Margileth and Kibler[242] as the youngest case of this type of sarcoma of the lung ever recorded. Treatment by surgery and cobalt was unsuccessful, and the patient died thirteen months after the onset of symptoms. An unusual case of a histiocytoma of the bronchus was reported in a six-year-old boy by Bates and Hull.[243]

In a clinical pathological conference of the Children's Medical Center in Boston, Massachusetts, two interesting cases were presented.[244] The first patient, who was diagnosed as having status asthmaticus, was found by means of bronchoscopy to have multiple transitional cell papillomata of the trachea. The second case presented was that of a nine-year-old boy with an eight-week history of an intermittent fever and cough. Bronchoscopy and bronchograms revealed a lesion of the left main stem bronchus which proved to be a bronchial adenoma.

The relationship of bronchiolitis to asthma was studied by Wittig, Cranford and Glaser.[245] As the authors pointed out in their introduction, the diagnosis of acute bronchiolitis is often enough fraught with vagueness, and the syndrome has been variously defined by different authorities. The criteria accepted by the authors for selecting cases of bronchiolitis with or without associated fine moist râles, a hyper-resonant chest, inconclusive hematographic findings and roentgenographic signs of obstructive emphysema with or without scattered parenchymal infiltrations. One hundred children diagnosed as having bronchiolitis were followed to ascertain how many of these children subsequently developed respiratory allergies and how many had a positive family history for allergy. It was found that thirty-two developed bronchial asthma while an additional seventeen developed other allergic respiratory disorders. The authors raised the question as to whether this high incidence of respiratory allergies (49 per cent) in children with a history of bronchiolitis could be of significance for an etiological relationship between bronchiolitis and asthma. The authors concluded that, irrespective of this relationship, acute bronchiolitis in infancy should alert one to the possible subsequent development of asthma. (In children under one year of age, it is extremely difficult at times to differentiate acute attacks of bronchiolitis from attacks of asthma precipitated by respiratory infections. The reviewers wonder whether some of the patients observed by the authors may not in reality have experienced their first attack of asthma. This may have, in part at least, contributed to the high incidence of subsequent development of allergic disease. Certainly the point made by the authors that a diagnosis of bronchiolitis should alert one to possible future development of allergic respiratory disease is worthy of emphasis.)

An acute epiglottitis can occasionally be mistaken for asthma as illustrated by the report of Berenberg and Kevy.[246] In the thirty-nine patients described, three of the children presented with symptoms of wheezing. (Under ordinary circumstances the differentiation is quite readily made. In the few cases where the acute epiglottitis may be atypical and mimic an acute attack of wheezing, it is imperative that the correct diagnosis be established as quickly as possible since acute epiglottitis represents one of the few real medical emergencies in pediatric practice.)

Croup, which is thought by some authorities to occasionally have an allergic etiology, can occasionally be confused with bronchial asthma. Philipson[247] discussed this syndrome and from his studies pointed out that croup is of a viral etiology in the majority of cases. (Recently an increasing number of different types of respiratory viruses have been isolated in patients presenting with the syndrome of croup.)

Until recently a disease characterized by diffuse interstitial fibrosis of the lungs (Hamman-Rich syndrome) and which can easily be confused with bronchial asthma was thought to occur only in adults. However, in 1956 Bradley[248] reported this condition in a nine-year-old child, and since then additional case reports of children with this disease have appeared in the literature.[249-251] The syndrome is characterized by cough, dyspnea, later cyanosis associated with minimal findings, is progressive in character and eventually leads to an asphyxial death. (Although admittedly rare, this disease, particularly at its onset, should be considered in the differential diagnosis of severe, unrelenting bronchial asthma associated with marked emphysema.) Donohue *et al*[252] have called attention to the fact that this "peculiar interstitial pneumonitis" may occur on a familial basis and described five infants from three families. Freud *et al*[253] described the use of steroids in the treatment of this condition.

Another condition which was previously described in adults, primary pulmonary obliterative vascular disease, has recently been observed in infants and young children. Husson and Wyatt[254] reported their studies of three young children with this condition. The clinical symptoms consist of marked dyspnea on slight activity, fatigue, chest pain, loss of consciousness or syncope, occasional cyanosis, cardiac enlargement, occasional murmurs and accentuation of the pulmonary second sound.

Cardiorespiratory syndrome of obesity has recently been observed in a child by Jenab, Lade, Chiga and Diehl.[255] The clinical features described consisted of marked obesity, polycythemia, dyspnea, intermittent cyanosis, somnolence, twitching, right ventricular hypertrophy and cardiac decompensation.

Two other diseases producing chronic pulmonary insufficiency of unknown etiology have been described. These should be considered in the differential diagnosis of bronchial asthma. Both of these conditions primarily occur in adults but have been reported in children. The first has been called pulmonary alveolar microlithiasis. The condition has a familial occurrence and a prolonged course leading to pulmonary insufficiency which occurs years after the recognition of the lesions roentgenologically—fine, sand-like particles spread uniformly throughout both lung fields. The most frequent symptoms are those of pulmonary insufficiency and shortness of breath on exertion. Sosman *et al*[256] in a sixty-five page article, summarized the twenty-one cases previously reported in the literature and reported three cases of their own. The other new syndrome recently described by Rosen *et al*[257] has been named pulmonary alveolar proteinosis. These authors reported a study of twenty-seven patients including two children. The condition is usually heralded by a febrile illness and is later manifested by dyspnea, cough, occasional yellow sputum, increased fatigue and loss of weight. The histologic and radiographic findings characteristic of this disease were described by these authors.

Certain other rare conditions that may occur in childhood and which must be considered in the differential diagnosis of asthma have been reported in the literature. Schoeniger[258] reported on a case of hemosiderosis and reviewed the clinical and roentgenographic picture of this disease. A syndrome consisting of slowly progressive ataxia beginning in late infancy, a progressive symmetrical scleral-cutaneous telangiectasia and the onset of chronic progressive lung disease at about school age was also described by Centerwall *et al*[259] and by Boder and Sedgwick.[260] The association of frequent pulmonary infections with dysautonomia was again emphasized by Stadler.[261] The hyperventilation syndrome was reviewed by Kilgour.[262]

Finally, diffuse fibrotic pulmonary changes have been described with the prolonged administration of hydantoin.[263]

COMPLICATIONS OF ASTHMA

Griffin, Kass and Hoffman[264] discussed cor pulmonale associated with symptoms and signs of asthma in children. They presented three cases which suggested a relationship between the two entities. Two of their three cases did not present any evidence of atopy. The authors emphasized that although studies of cardiopulmonary function should be done in all children suffering from bronchial asthma, it is essential that the cardiac status be evaluated whenever a patient with asthma is responding poorly to treatment or evidence of decreased pulmonary function is found.

The relationship of bronchiectasis to allergy has been discussed by several authors. It was Lipschutz's[265] feeling that bronchiectasis is more common in children than generally recognized and that allergic diseases are frequently the underlying factors "in setting off this disease." In order to rule out bronchiectasis, which is frequently difficult to recognize in children because the symptoms are minimal and masked by antibiotic therapy, the author suggested that all children with respiratory allergy be investigated for bronchiectasis. (Although in recent years the risk of doing bronchograms has become minimal and the techniques for performing the procedure simplified, the reviewers are still of the opinion that bronchograms should be undertaken only in those patients in whom bronchiectasis or some other lung pathology is suspected which might be delineated by this procedure.) Lipschutz was of the opinion that bronchiectatic changes in lungs could be reversed when adequate treatment for the allergic manifestations and infections was instituted early. Nelson and Christoforidis[266] likewise reported such reversible changes in bronchiectasis with medical management. Goldman[267] further called our attention to the fact that bronchiectasis and allergic respiratory disease are often coexistent. He emphasized that before considering pulmonary surgery, the allergic factors should be recognized and managed.

Williams and O'Reilly[268] in a study of children pointed out that bronchiectasis should be regarded as the end stage of a number of distinct diseases. The clinician by recognizing the early stages of these diseases may be able by appropriate therapy to prevent permanent pulmonary damages and bronchiectasis. The technique of bronchography in children was evaluated by Bovornkitti and Zabriskie.[269]

The complication of atelectasis of the entire left lung was reported by Cantonnet and Barani[270] in a nine-year-old child with asthma.

Other unusual complications of asthma, which have been described in adults, were xiphidynia[271] and repeated multiple fractures of the ribs.[272]

The treatment of respiratory failure secondary to chronic pulmonary emphysema has been discussed by several different authors.[273-275] Although these workers were mainly concerned with adult patients, the principles they described may well be applied to pediatric patients.

ADRENOCORTICAL HORMONES AND CORTICOTROPIN

As one might expect, a great many papers have been published on the adrenocortical hormones and corticotropin as related to their use in the diseases of hypersensitivity. Much of this literature concerns further experiences with the more prolonged use of the older steroid preparations and the effects of the newer synthesized hormones (whose virtues, in the review-

er's opinion, have been prematurely extolled by many of the investigators). As an introduction to this subject, the impressions left by the New York Academy of Science Conference, marking the ten-year anniversary of the administration of cortisone to a patient, are worthy of restatement.[276] First, corticosteroids have brought forth some benefits in the treatment of some medical disorders. Secondly, dexamethasone and other of the newer steroids are not the "ideal anti-inflammatory" steroid devoid of side effects. Finally, the mechanism of action of these compounds remains unknown.

The pharmacophysiologic principles in the use of corticoids and adrenocorticotropin have been presented by several different authors.[277-280]

Bongiovanni, Mellman and Eberlein[281] reviewed our current knowledge of the use of adrenal hormones and corticotropin in the pediatric age group. In addition to the pharmacophysiologic effects of these agents, they discussed their indications in the pediatric age groups, described the various hormonal preparations available, suggested dosages for each, made some general recommendations for therapy with the hormones, and reviewed the complications arising from their use. Because of the importance of some of the general recommendations advocated for steroid and ACTH therapy by the authors, they are herewith again stated in an abbreviated form. (1) The indication and response desired by the physician must be well defined before starting therapy. (2) Use the smallest possible dose for maintenance. (3) Tapering the dose is important upon withdrawing hormone therapy. (4) Acceptance of partial suppression of the manifestations of an inflammatory disorder. (5) Awareness of all possible complications and their prevention at their onset. (6) Avoid their use if the child is exposed or known to have certain infections, e.g., tuberculosis, chicken pox. (7) Careful supervision to avoid unsuspected complicating infections. The general metabolic effects of these agents in adults were discussed by Thorn, Renold and Winegrad[282] and in the neonate by Migeon.[283]

The effects of cortisone on antibody response to influenza-virus vaccine in children with nephrosis was studied by Kunin *et al.*[284] These authors found that antibody response, as measured by the hemagglutination-inhibition test two weeks following a single subcutaneous dose of influenza-virus vaccine, was not significantly different in children with active or inactive nephrosis, and appeared to be similar in those receiving hormone therapy and in those who were not.

Levin and Adler[285] described their experience with the use of steroids in the treatment of eighty-five allergic children. In the patients over five years of age, treatment was started with 10 to 20 mg of prednisone daily in divided doses for the first four days; the dose was decreased to 5 mg on the fifth day and subsequently lowered to 2.5 mg per day for the final two days. In younger children, less prednisone was used initially and the dose tapered in a similar fashion. The authors concluded that prednisone for short-term therapy is uniformly successful for alleviating acute episodes of the various allergic states, facilitates earlier allergic investigation and enables long-term hyposensitization therapy to continue uninterrupted. The authors also emphasized these hormones should not be used as a substitute for proper allergic management. The use of steroids in allergic children has also been evaluated by Copello,[286] Perrotta[287] and by Logan.[288]

The usefulness of the corticosteroids in the treatment of status asthmaticus and severe, incapacitating, chronic asthma remains unchallenged. Thursby-Pelham and Kennedy[289] compared prednisolone with cortisone in the treatment of children with chronic asthma by measuring the ventilatory function before and after the administration of each of these drugs. They concluded

that the general effects and relief of symptoms produced by the two drugs were similar, though 15 mg of prednisone gave better results than 75 mg of cortisone. Irwin and Burrage[290] discussed the principles of dosage, destiny of patients and serious illnesses encountered with the use of adrenal cortical steroids in the treatment of intractable bronchial asthma. They concluded that these agents are effective, but their use on a maintenance basis should be reserved only for those patients with asthma of undetermined etiology of such severity as to threaten life or to cause chronic invalidism.

Brockbank *et al*[291] discussed the long-term treatment of severe bronchial asthma with oral cortisone and suggested that this drug should be given initially on a short-term basis. They made the statement that in their experience cortisone given during pregnancy did not have any deleterious effect on the mother or the child. (There is some evidence both in animals and in man that the administration of corticosteroids during pregnancy does have some untoward effects on the infant. Millen and Woollam,[292] for example demonstrated that cortisone enhances the teratogenic effects of hypervitaminosis A in rats. In man Laron[293] presented a case report of a baby born to a mother with the adrenogenital syndrome treated with hydrocortisone 100 mgs every fourth day for a period of three and one-half years. Although no congenital abnormalities were noted, there was some evidence of adrenal insufficiency demonstrated in the infant.)

Brown[294] correlated the use of prednisolone in the treatment of refractory asthma with the number of eosinophils in the sputum. It was his conclusion that the prednisolone was more effective where the sputum showed large numbers of eosinophils. Franklin et al[295] observed that the combined use of corticosteroids with bronchodilators was of definite value in the therapy of obstructive pulmonary emphysema.

Several authors have reported favorable results with the use of different types of corticosteroid aerosol preparations. Peters and Henderson[296] used an aerosol of prednisolone phosphate which appeared to be well tolerated. Because ten of eleven asthmatic patients derived benefit from treatment with this preparation, the authors concluded that this form of therapy may prove to be a useful adjunct in the management of asthma and that it merited further trial for a more definite evaluation. Aerosol preparations of prednisolone and hydrocortisone suspended in a Freon propellant were used by Franklin *et al*.[297] Using a double-blind technique, they concluded that this preparation produced a topical therapeutic effect in asthma, approximately equivalent to a daily dose of 40 mg of hydrocortisone given by mouth. In another double-blind control study, Helm and Heyworth[298] concluded that the inhalation of hydrocortisone acetate in a fine powder was of significant benefit to the patients. However, in another investigation, these same authors found that this form of therapy was of very little benefit in patients with chronic bronchitis.[299] In separate studies, favorable results with powdered hydrocortisone or prednisolone or with an aerosol of prednisolone were similarly reported by Herxheimer *et al*;[300] Brockbank and Pengelly;[301] Hajos;[302] and Massara and Teatini.[303]

On the other hand, in the only study performed with children, Smith[304] found the use of hydrocortisone hemisuccinate by inhalation to be disappointing. Fifty-seven asthmatic children were furnished with either a placebo mixture or a solution containing hydrocortisone to be taken daily by inhalation for the relief of their asthma. Neither the patient nor the doctor was aware of the identity of the solutions used for therapy. The same amount of solution was inhaled daily for one month, and the effectiveness of the treatment was judged by a daily symptom record kept by the mother

of each child and also by weekly computation of the volume of expired air the first 0.75 second. Subjective and objective results of a month's trial therapy disclosed that 14 per cent appeared to be benefited by the placebo and twenty-one per cent by the hydrocortisone inhalation. These findings were not regarded as being statistically significant by the authors. (In view of the many favorable reports of the use of aerosol preparations in adults, this form of therapy in the treatment of asthma in children would seem worthy of further investigation.)

To test the thesis that intravenously administered steroids might shorten the time required to obtain relief from asthma, Pinkerton and Van Metre[305] compared the rapidity of prednisolone intravenously, prednisolone orally, and epinephrine intramuscularly. The response to the therapeutic agent tested was measured by frequent questioning, physical examinations and determinations of the vital capacity over a period of two to three hours. The results indicated that epinephrine is more rapidly effective against asthma than prednisolone administered orally or intravenously. The authors also concluded from their data that prednisolone and epinephrine do potentiate their respective effects on asthma. (The results of this experiment certainly confirm what has been observed clinically and are not surprising in view of the evidence that the effect of epinephrine is sympathomimetic and that of prednisolone anti-inflammatory.)

Madsen *et al*[306] compared the steroid hemisuccinates with the corresponding free steroids in regard to their effects on circulating concentrations of free (nonsterified) 17-hydroxycorticosteroids when administered intravenously to normal human subjects. The plasma 17-hydroxycorticosteroid concentrations thus produced were lower than those produced by equivalent doses of free steroids in alcoholic solutions. From their data the authors concluded the steroid hemisuccinate esters would be effective clinically, but that the dose required to produce equivalent blood levels of free steroids would be somewhat higher for the hemisuccinate esters of steroids than the parent compound.

Several general reviews have appeared in regard to the use of the corticosteroids in the treatment of skin diseases.[307-310]

The corticosteroid topical preparations have been established as being extremely beneficial, even in small doses, in the management of a wide variety of common dermatoses. In an editorial on the use of topical steroids, Jackson[311] made the following points: (1) As with all intelligent medical therapy, diagnosis is essential. (2) In many conditions the action of topical steroids is only suppressive, not curative. (3) Attention to the usual dermatological therapy is required. (4) The type of vehicle must be appropriate to the stage and location of the dermatitis. (5) For most conditions, a 0.5 per cent strength of hydrocortisone is adequate.

There has been some evidence presented that some of the newer steroids applied topically are more effective than hydrocortisone. For example, triamcinolone in a concentration of 0.1 per cent has been demonstrated to be more effective than 1 per cent hydrocortisone.[312-315] (In a limited number of patients, the reviewers similarly found 0.1 per cent triamcinolone to be at least equally effective as 1 per cent hydrocortisone for the treatment of atopic dermatitis.) In contrast to some of the aforementioned studies, Grayson and Shair[316] felt that the topical use of 0.5 per cent methyl prednisolone was no more effective than 1 per cent hydrocortisone in the treatment of atopic dermatitis. Robinson[317] recommended the use of a prednisolone aerosol for local therapy of dermatoses. He felt that this type of preparation was especially useful for inflammatory lesions involving large

surface areas and regions of the body which contain large amounts of hair. He also believed it to be more effective in relieving pruritus than either steroid creams or ointments.

Because of the many beneficial claims made for some of the newer synthetic corticosteroid preparations, a review of some of the papers published on the specific drugs seems warranted. Studies mentioned elsewhere in a discussion on the steroids, even though concerned with a certain type of hormone, will not be included in this discussion.

Prednisone and Prednisolone

Bukantz and Aubuchon[318] discussed the principles of management of allergic disorders by means of prednisone and prednisolone with special emphasis on the clinical and laboratory control of serious complications. Gregoire and Rose[319] reviewed their experience in the clinical use of prednisone and prednisolone in 146 cases of allergic diseases. As has been established by many investigators, these authors found prednisone and prednisolone to be three to five times more potent therapeutically than cortisone and free of effects on salt and electrolyte metabolism when administered in therapeutic doses. These hormones were also used by Sherwood and Barnard[320] in the treatment of fifty-eight patients with various allergic disorders. Eighty-one per cent of these patients could be controlled with 15 mg or less of these agents, while nineteen per cent of their subjects required 20 to 40 mg per day.

Methyl Prednisolone

Methyl prednisolone was reported by Wygant[321] as useful in the treatment of bronchial asthma. Some of the side effects of this drug were studied by McMahon and Gordon[322] in sixty-seven patients and in ten healthy volunteers. The dose administered varied between 4 and 42 mg per day given over a period of a few days to seven months. Fourteen patients were noted to develop obesity on doses exceeding 12 mg per day when given for periods of two or more months. Other complications noted were bloating and dyspepsia, reactivation of duodenal ulcer in one patient, mild personality changes and one instance of chronic hypercortisone syndrome consisting of increased fatigue, emotional instability and generalized muscular and joint pains.

Triamcinolone

Several authors have reported on the favorable effects of triamcinolone in the treatment of allergic disorders.[323-326] In a study of the side effects following the administration of triamcinolone to forty-seven patients, Kendall and Hart[327] noted that twenty-four patients had experienced some serious side effects, the majority of which resembled those noted with other steroids. Four patients suffered "muscle-wasting," the cause of which was not apparent to the authors. (Some of the previously mentioned papers also stressed weakness and muscle cramps which is noted more frequently with the administration of this particular steroid preparation.) An unusual complication, arthritis, was noted in three patients following the administration of triamcinolone by Wells.[328]

Dexamethasone

The last and the most potent of the newer synthetic corticosteroids to become available commercially was dexamethasone. Following the initial report by Boland[329] on its use as an anti-rheumatic drug, a great many papers

have been published with reference to its use in allergic diseases.[330-342] (Most of these authors concluded that this hormone was as effective in the management of allergic diseases as some of the earlier synthesized hormones. In general it was found that 0.75 mg of dexamethasone was clinically equivalent to 5 mg of prednisone or prednisolone. Most of the complications and side effects that have been observed with other steroids can follow the administration of dexamethasone; moon facies and increased weight gain being particularly common side effects of this drug. Until it can be demonstrated that the long-term use of these newer, more potent synthetic hormones does in reality produce fewer side effects, the reviewers, except under experimental circumstances, would prefer to continue the use of prednisone or prednisolone in instances where these hormones are indicated.)

Steroid Combinations

The use of steroids in combination with a tranquilizer or an antihistamine has been the subject of several reports. Brown and Seideman[343] and also Fox[344] concluded from their studies that the combination of prednisolone with hydroxyzine was more effective than either prednisolone or hydroxyzine given separately. Arbesman and Ehrenreich,[345] on the other hand, concluded that the majority of allergic persons did not appear to be benefited by the addition of a tranquilizer to a maintenance dose of corticosteroids.

The combination of a corticosteroid and an antihistamine were also thought to have synergistic effects by Grater,[346] Lackenbacher,[347] Macaulay,[348] and MacLaren.[349] (In the administration of such potent agents as the steroids, the reviewers prefer not to use these drugs in combination with other preparations such as antihistamines and tranquilizers for several reasons. First, dosages of the individual constituent drugs cannot be controlled. Secondly, one of the individual drug components may be contraindicated in the particular disease or patient. For example, antihistamines are usually not considered good therapy for moderately severe attacks of asthma. Finally, the reviewers would like to caution against the use of systemic steroids, even though used in relatively small quantities for such conditions as allergic rhinitis and allergic conjunctivitis.)

Complications From Steroids

The potential dangers from these drugs are exemplified by the description of many new types of serious reactions in addition to numerous reports of "older" well-recognized untoward effects. These latter effects were generally discussed by Chute[350] and also by Weir.[351]

In order to obviate some of the untoward effects of hormone administration, Siegel *et al*[352] evaluated a schedule of intermittent prednisolone therapy in the treatment of forty-two children with severe allergic disorders who had failed to respond to ordinary allergic management. This schedule consisted of administering prednisolone for three successive days of each week followed by a four-day rest period, the initial dose usually being 15 to 30 mg per day given in two to three divided doses and the subsequent dose tapered with clinical improvement. An appraisal of adrenocortical function was studied in the majority of the subjects by measuring the increase in the level of circulating 17-hydroxycorticosteroids in response to the administration of exogenous ACTH and by measuring the urinary excretion of adrenocorticosteroids. The data showed that intermittent therapy did cause definite depression of adrenocortical response, and although there was partial recovery of the pituitary-adrenal function during the four-day rest period,

there was some residual impaired activity of the gland. It was therefore suggested that patients on intermittent therapy during periods of stress should receive some supplemental steroids and revert to continuous steroid maintenance therapy at these times. The authors also concluded that although a schedule of intermittent steroid therapy was found to be useful as an adjunct in the treatment of intractable asthma and atopic dermatitis, it should not be used as a substitute for conventional methods of treating allergic patients.

Numerous deaths from adrenal insufficiency in patients who had received steroids and who were subjected to some form of stress have been reported in the literature. Johnson and Fuller[353] presented an additional case report of a patient whom they believed died from adrenal insufficiency secondary to the administration of cortisone.

The intermittent administration of ACTH has been occasionally advocated as a means of circumventing adrenocortical depression by the administration of steroids. A consultant, in answering a question of this nature, stated that there is no clinical or experimental evidence to support such use of ACTH and that it would be unwise to rely on intermittent administration of ACTH as a means of avoiding problems which may be associated with adrenal depression by the steroids.[354]

Growth suppression as a result of the administration of prednisone and methyl prednisolone has recently been studied by Van Metre and Pinkerton.[355] These authors noted a growth suppression in twelve of thirteen asthmatic children receiving these drugs for six months or longer. Cessation of therapy or deduction of average dosage below the critical growth-suppressive level (5.1 mg per square meter of body surface per day) was followed by the appearance of a normal or accelerated growth rate.

An increased susceptibility to bacterial and viral infections has long been recognized as a serious complication of the steroids. Opinions ranging from their use during acute infections to complete withdrawal have been advocated by a number of investigators. In an editorial[356] on the use of adrenocortical hormones in infections, the editor concluded that the "best evidence thus far has failed to demonstrate any life-saving effects from these hormones in cases of bacterial meningitis and even suggests that complications may be actually increased rather than decreased, and the active disease prolonged rather than shortened when adrenocortical steroids are used."

The problem of management of a patient who is receiving steroids and who develops an infection such as chickenpox has not been satisfactorily answered. Adding to the previously reported clinical and experimental studies, Nichols[357] reported three additional cases of varicella occurring in children receiving steroids. Although autopsies and viral studies were not obtained, the author attributed the demise of two of these patients to the enhancement of the varicella infection by the hormones. The third patient had his cortisone dose of 100 mg reduced to 25 mg during the infection and experienced a mild course. The author suggested that in patients who developed chickenpox or measles while they were receiving high doses of steroids that the dose be immediately reduced to an estimated "physiologic stress level" of steroids. (The reviewers have followed a similar type policy in the management of children receiving steroids who have developed varicella infections.) On the other end of the scale are such reports as Thompson and Cantrell's[358] who suggested the use of prednisolone in the treatment of varicella pneumonia. The authors believed that the administration of this hormone in one case was responsible for carrying the patient over the critical phase of her illness.

The problem of staphylococcic infections occurring with long-term use of prednisone was briefly discussed by Kanee and Mallek,[359] and three case illustrations were presented. The increased susceptibility to fungus infections associated with the administration of steroids was discussed by Torack.[360] He theorized that the decrease in inflammatory response, diminution in onset, intensity and duration of endothelial sticking of leukocytes, diminished phagocytosis or digestion of phagocytosed material, decreased antibody response, and possible depression of the reticuloendothelial system *per se* accounted for the effects of steroids on infection.

During the past couple of years pancreatitis has been recognized as a serious complication of corticosteroid therapy.[361-365] The mechanism of this action remains obscure; it has been suggested, however, that due to changes in viscosity of the pancreatic secretions, obstruction of the gland might occur. Infection as a possible cause has not been excluded. In a general review of acute pancreatitis in children, Stickler and Yonemoto[366] described the case histories and findings at autopsy of three children dying suddenly after they had received prolonged courses of steroid hormones. One of these patients was a sixteen-year-old girl suffering from severe asthma who had been receiving cortisone for five months previous to death. Although the clinical course of these patients did not quite follow the typical pattern described for acute pancreatitis, all three were found to have extensive necrosis of the pancreas and the immediate surrounding fat tissues.

Reports of gastrointestinal complications as the result of steroid administration continue to appear in the literature. Lorber[367] reported the case of a massive haematemesis in a fourteen-year-old girl treated with prednisolone for a three-and-a-half-month period. He suggested that a combined routine antacid treatment with cortisone or prednisolone therapy be adopted in children even though ulcers and gastrointestinal bleeding are rare complications of steroid therapy. Boland and Headley[368] similarly advised the use of antacids to reduce the digestive disturbances in patients treated with prednisone and prednisolone. In an uncontrolled preliminary study, West[369] recommended the use of an enteric-coated prednisolone tablet to prevent gastric symptoms in patients receiving corticosteroid therapy.

Although all three cases reported by Lockey[370] were adults, the reviewers thought the allergic reactions noted in these patients from the ingestion of dexamethasone (both 0.5 mg Decadron® and 0.75 mg Deronil®) and prednisolone (5.0 mg Paracortol®) was of sufficient interest to be included in this pediatric review. All three of the subjects had immediate urticarial reactions following the ingestion of one of the aforementioned corticosteroid hormones. Common to all of these preparations is the aniline dye tartrazine, also known as FD&C yellow No. 5, used to color and identify these agents. This dye is known to be a sensitizing substance and was incriminated in Lockey's patients by positive tests with 1 cc dose of a 1:1000 dilution of tetrazine administered sublingually in two of the subjects and by the administration of a non-colored dexamethasone tablet without untoward effects in the third patient. (It has recently been shown experimentally that several of the steroid hormones may act as haptens when coupled to a protein and that antibodies with steroid specificity may be elicited.[371] Thus it is conceivable that allergic reactions could occur from hormones themselves; however, the reviewers have never observed or seen any reference to such a reaction in the literature.)

Another unusual syndrome, pseudotumor cerebri, has been postulated by Dees and McKay[372] to be a complication of prolonged steroid therapy. They

noted the development of benign intracranial hypertension in three young boys with asthma who were receiving small doses of adrenal steroids during withdrawal treatment. These patients had received continuous steroid therapy for several years and had acquired the appearance of Cushing's disease. The mechanism by which pseudotumor cerebri developed in these three children was not determined. Among the possibilities discussed were an allergic reaction; electrolyte imbalance; reaction to hypoxia; a bizarre reaction to dehydration, infection or head trauma; or a possible complication of prolonged use of steroid therapy. They considered the latter as the most likely etiology.

Additional complications reported in the literature were hemorrhagic skin manifestations,[373] nodular panniculitis,[374] psychic and somatic changes in allergic children,[375] and bascular lesions.[376,377]

Some investigators have suggested that since the advent of the steroids there has been an increasing number of deaths from asthma as a result of the use of these hormones. In refuting this concept, Williams[378] presented a graph to show that although in 1951 there was an increased number of deaths from asthma, a similar increase in deaths was noted from other respiratory illnesses, such as pneumonia and bronchitis. He also demonstrated there was a decrease in the death rate from asthma in subsequent years, which he attributed to the use of steroids.

Corticotropin

Schwarz[379] presented a comprehensive review of the literature on the important qualitative differences in the modes of action of ACTH and of cortisone and its analogues. Certain advantages of ACTH were pointed out by the author as follows: (1) It does not cause atrophy of the adrenal cortex. (2) Withdrawal symptoms are less frequently encountered. (3) It appears to be less catabolic than oral steroids in therapeutic dosages. (4) It will influence favorably some diseases incompletely controlled by oral steroids. It was Schwarz's impression that the undesirable effects of adrenal atrophy produced by oral steroids can be avoided by combining them with intermittent administration of ACTH.

Siegel *et al*[380] in a study to determine the potency and duration of activity of zinc-ACTH and gel-ACTH, measured the circulating plasma of 17-hydroxycorticosteroid levels, the urinary excretion concentrations of 17-hydroxycorticosteroids and 17-ketosteroids, and the eosinopenic response following the administration of each of these preparations. The data from their studies indicated that zinc-ACTH is longer acting than gel-ACTH but its activity is less than twenty-four hours. Members of the Research Council of the American Academy of Allergy similarly compared zinc and gel-ACTH.[381] Their findings indicated that these preparations had approximately equal therapeutic effectiveness but could not uniformly demonstrate an increased duration of activity from a single dose of corticotropin zinc.

One of the serious disadvantages of ACTH, other than the necessity of its being administered parenterally, is the severe hypersensitivity reactions which may result from its use. Charpin and Zafiropoulo[382] reported eleven allergic patients who developed reactions following the administration of ACTH. These authors presented evidence which indicated that the patients were allergic to protein present in all pituitary extracts regardless of their functional specialization or their animal origin. Galin[383] reported a case of unilateral adrenal hemorrhage during ACTH therapy.

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(To be continued in the February issue)

The Shape of Things to Come

Studies on the nature of antibody production during the in vitro culture of lymphoid tissues.
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The effect of electric stimulation of the brain on anaphylactic shock in guinea pig.
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Edna Z. Mortimer, J. Pediat., 58:90 (Jan.) 1961.

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News Items

AMERICAN ORTHOPSYCHIATRIC ASSOCIATION

The American Orthopsychiatric Association Inc. will hold its thirty-eighth annual meeting at the Hotel Statler-Hilton, New York City, from March 22 to March 25, 1961. A primary topic of discussion will be the treatment of asthmatic children in a residential program.

EUROPEAN ACADEMY OF ALLERGY

The European Academy of Allergy will hold its annual meeting in Berlin, Germany, on April 28 and 29, 1961. According to the Academy's provisional program, the main topic on April twenty-eighth will be differential diagnosis of bronchial asthma and destructive emphysema of the lung. The speakers on this subject will be Professor Gough of Cardiff, Professor Orie or Groningen, and Doctor Scherrer of Bern.

Professor Stuttgen of Dusseldorf, Doctor Schnyder of Zurich, and Doctor Dorn of Berlin will speak on neurodermatitis and contact eczema on April twenty-ninth.

Additional lectures and demonstrations are scheduled for the afternoon sessions of both April twenty-eighth and twenty-ninth. Further details of the meeting may be obtained from Priv.-Doz. Dr. Michel, Berlin-Charlottenburg 9, Krankenanstalten, Westend.

CHICAGO SOCIETY OF ALLERGY

The newly elected officers of the Chicago Society of Allergy for the year 1960-1961 are as follows:

Bert B. Schoenkerman, M.D., President
Charles M. Jenkins, M.D., President-Elect
Abe Matheson, M.D., Secretary-Treasurer

NEW YORK ALLERGY SOCIETY

New officers of The New York Allergy Society for 1960-1961, elected at the annual meeting, November 16, 1960, are as follows:

President—Joseph H. Fries, M.D.
President-Elect—Sheppard Siegal, M.D.
Vice President—Murray Dworetzky, M.D.
Secretary—Ely Perlman, M.D.
Treasurer—Walter Kessler, M.D.
Assistant Secretary-Treasurer—Bernard Siegel, M.D.

Papers of Interest

Portwich, F., and Marcon, H.: Lethal allergic thrombopenia after influenza prophylaxis with phenyl mercury borate. Aerztl. Wochenschr., 14:65, 1959.
Lethal thrombopenia starting fourteen days after treatment with phenyl mercury borate. The same agent had been taken some time before. No other therapy had been given. Prausnitz-Kustner test was positive. A.J.W.

Hajós, M.: Hay Fever in Hungary, Hétilap, 99:1185, 1958.
Hay fever in Hungary has two main seasons, namely May-June (due to the pollens of acacia and rye) and July-August (mostly due to grass pollen). A.J.W.

Lyon, E.: Amoebiasis and allergy. *Allergia u. Asthma*, 4:289, 1958.
Allergic sensitization after infection with *Entameba histolytica* is suggested by the occurrence of eosinophilia, urticaria, asthma, affection of the joints. A.J.W.

Bruun, E.: Quincke's edema from the view point of allergy. *Allergia u. Asthma*, 4:216, 1958.
In 128 cases out of 227 cases (56 per cent) of Quincke's edema, an allergic genesis could be established. Drugs, particularly preparations of acetylsalicylic acid, were inculpated in seventy-five cases, food in thirty-nine, contact or respiratory allergens in thirteen, and physical allergy (cold) in one.

Kirchmair, H.: Thrombopenia during doriden medication. H. Mediz. Klinik., 39:1683, 1958.
Report of a case, where after four week's medication with two tablets daily of Doriden (glutethimite) a thrombopenia was observed. The count had returned to normal after seven weeks. A.J.W.

Hydovitz, J.: Occurrence of goiter in an infant on a soy diet. New England J. Med., 262:351 (Feb. 18), 1960.
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Robbins, J. J.: Treatment of intractable bronchial asthma; results in twenty-two cases. Am. Practitioner, 10:2135 (Dec.), 1959.
Prednisone in doses of 10 mg or less administered daily to twenty-two asthmatic patients, rehabilitated fourteen and helped the other eight with no observable ill effects within three to thirty-six months.

BOOK REVIEWS

ALLERGIE UND ALLERGISCHE ERKRANKUNGEN. By E. Rajka, Vol. I, 638 pages, $15.00, Vol. II, 1003 pages, $18.00, 1959, Budapest: Publishing House of the Hungarian Academy of Sciences, Hungary.

This work, published in two volumes by the Hungarian School of Allergists, is a most comprehensive and valuable handbook on the principles of allergy and allergic diseases. It should be read by everyone interested in allergy and immunology who reads German.

Volume I deals with the theoretical aspects of allergy and its close relationship with immunology. The chapter on the immediate and delayed types of allergic reactions is excellent. Such subjects as the immunochemistry of antigens and antibodies, the biochemistry of neuroallergic reactions and serology are dealt with in great detail and contain the latest information on these subjects.

Volume II is the clinical part of this work. Every aspect of clinical allergy is covered: the respiratory tract, the gastrointestinal tract, the cardiovascular system, allergy of the kidneys, immunohematology, auto-allergy, as well as the relationship between allergy and tuberculosis, syphilis, and collagen diseases. Those interested in microbial allergy will enjoy reading Korossy's scholarly chapter on microbial eczema.

The illustrations are well chosen and excellently reproduced. Each chapter has an up-to-date reference list of the world literature.

H.B.

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